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From Palladium to Iron: Towards More Sustainable Catalysis

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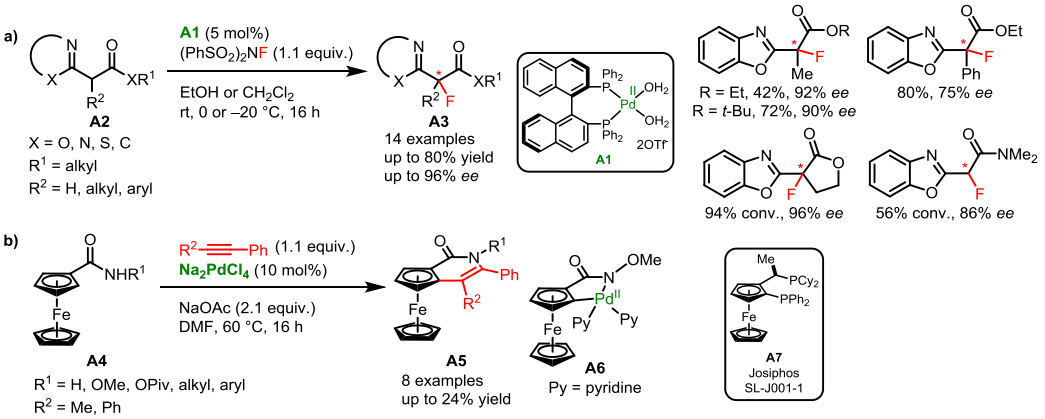
Abstract

The construction of bonds in a controlled and selective manner and the development of operationally simple, general and reliable methods to achieve these aims remains a key goal of chemical synthesis and the countless industries it impacts upon. With this in mind, the chemo-, regio- and stereoselective introduction of a number of functionalities into small molecules was investigated.

Traditionally the majority of functionalisations have used precious metals; the scope of transformations that can be achieved using these catalysts is remarkable. Palladium in particular has found widespread application in new bond-forming processes and, in addition to cross-coupling reactions, palladium catalysis has been used to effect a wide variety of asymmetric reactions.

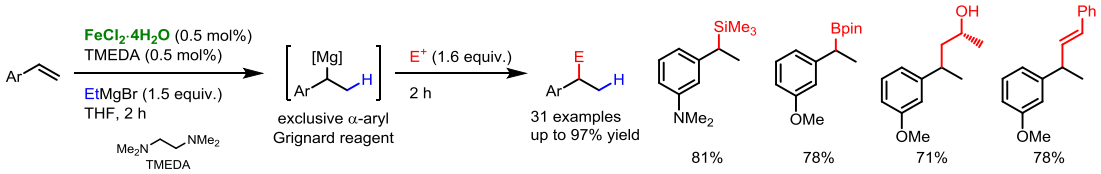
This work describes investigations into the palladium-catalysed enantioselective electrophilic fluorination of azaarylacetates and amides **A2** and the oxidative annulation of ferrocene derivatives **A4** (*Scheme A1*). Both products have structural significance; heterocycles and stereogenic fluorinated centres, present in **A3**, are important motifs in the pharmaceutical industry, and ferrocenes are important rigid scaffolds in chiral ligands such as those in the Josiphos family e.g. **A7**.



Scheme A1. Palladium catalysis for **a)** enantioselective fluorination and **b)** oxidative annulation

Whilst a general catalyst remained elusive for the asymmetric fluorination of azaarylacetates and amides, benzoxazole-containing substrates were consistently fluorinated with excellent enantioselectivity (up to 96% *ee*) using palladium catalyst **A1** (*Scheme 1a*). The oxidative annulation of ferrocene derivatives proved challenging and although the reaction was successful, the product could only be isolated in up to 24% yield (*Scheme 1b*). In order to determine the yield-limiting step of the reaction, mechanistic studies were conducted and palladacycle **A6** was synthesised as a possible reaction intermediate.

Recently there has been a shift towards the development of more sustainable, environmentally benign and economic catalyst systems and iron is quickly becoming recognised as a viable alternative owing to its high natural abundance and low toxicity. A general iron-catalysed hydrofunctionalisation procedure is described that was used to form a wide variety of carbon-carbon and carbon-heteroatom bonds (*Scheme A2*).



Scheme A2. Iron catalysis for carbon-carbon and carbon-heteroatom bond formation

With just 0.5 mol% iron catalyst, the broad scope formal hydrofunctionalisation of styrene derivatives was achieved using commercially available and bench-stable catalysts and reagents. An iron-catalysed highly regioselective hydromagnesiation gave a common benzylic Grignard reagent, which was reacted with an array of electrophiles in a highly chemo- and regioselective manner. Significantly, the products of formal hydroboration, hydrosilylation and cross-coupling reactions were obtained.

Declaration

I certify:

a) that the thesis has been composed by me, and

b) either that the work is my own, or, where I have been a member of a research group, that I have made a substantial contribution to the work, such contribution being clearly indicated, and

c) that the work has not been submitted for any other degree or professional qualification except as specified.

Alison S. Jones

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Contents

Abbreviations

Ac	acetyl
acac	acetylacetonate
Ar	aryl
BAr^F_4	tetrakis(pentafluorophenyl)borate
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BIP	bis(imino)pyridine
BIPHEP	2,2'-bis(diphenylphosphino)-6,6'-dimethoxy-1,1′-biphenyl
bipy	2,2'-bipyridine
Bn	benzyl
Boc	di-*tert*-butyl dicarbonate
BOX	bis(oxazoline)
COD	1,5-cyclooctadiene
COE	cyclooctene
Cp	cyclopentadienyl
Cp*	pentamethylcyclopentadienyl
CPME	cyclopentyl methyl ether
Cy	cyclohexyl
DABSO	1,4-diazabicyclo[2.2.2]octanebis(sulfur dioxide) adduct
dba	dibenzylideneacetone
DBFOX	(dibenzofuran-4,6-diyl)-2,2'-bioxazoline
DCC	*N*,*N*'-dicyclcohexylcarbodiimide
DCE	1,2-dichloroethane
de	diastereomeric excess
DFT	density functional theory
DG	directing group
DHQB	dihydroquinine-4-chlorobenzoate
DIAD	di-*iso*-propyl azodicarboxylate
DiPAMP	1,2-bis[(2-methoxyphenyl)(phenylphosphino)]ethane
DMA	*N*,*N*-dimethylacetamide
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMDP	dimethyldiphenyl
DMSO	dimethyl sulfoxide
DoM	directed *ortho*-metallation
DPEN	1,2-diphenyl-1,2-ethylenediamine
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
ee	enantiomeric excess
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ehx	2-ethylhexanoate
EI	electron impact
equiv.	equivalents
ES	electrospray ionisation
EWG	electron withdrawing group
Fc	ferrocene
hexaPHEMP	4,4',5,5',6,6'-hexamethybiphenyl
HMDS	bis(trimethylsilyl)amide
HOMO	highest occupied molecular orbital
IPr	1,3-bis(2,6-di-*iso*-propylphenylimidazole-2-ylidene)

LB	Lewis base
L	ligand
LDA	lithium di-*iso*-propylamide
L-selectride®	lithium tri-*sec*-butylborohydride
LUMO	lowest unoccupied molecular orbital
M	metal
MOM	methoxymethyl
Ms	methanesulfonyl
MS	molecular sieves
NFOBS	*N*-fluoro-*O*-benzenedisulfonimide
NFSI	*N*-fluorobenzenesulfonimide
NMP	*N*-methylpyrrolidine
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NP	nanoparticle
Ox	oxazoline
Piv	trimethylacetyl
PHOX	phosphinooxazoline
pinacol	2,3-dimethyl-2,3-butanediol
py	pyridine
R_f	retention factor
SCE	standard calomel electrode
SEGPHOS	5,5'-bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole
Selectfluor®	1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane-bis(tetrafluoroborate)
S_N2	nucleophilic substitution, bimolecular
S_NAr	nucleophilic aromatic substitution
TADDOL	*α,α,α,α*-tetraaryl-1,3-dioxolane-4,5-dimethanol
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TBME	*tert*-butylmethyl ether
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TMDP	tetramethyldiphenyl
TMEDA	*N*,*N*,*N*',*N*'-tetramethylethylenediamine
TMS	trimethylsilyl
t_r	retention time
TRIP	3,3'-bis(2,4,6-tri-*iso*-propylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate
Ts	*para*-toluenesulfonyl
TS	transition-state structure
UV	ultraviolet

Chapter 1. Introduction

Palladium and iron are two highly valued metals, each with its own unique properties but increasingly overlapping applications. Palladium is primarily used in catalytic converters with minor applications in jewellery, electronics, dentistry, and chemistry[1] yet the relatively high cost and limited supply of the metal is a growing concern for many industries.[2] Recently, there has been a drive towards the use of more sustainable metals, for example iron, which are not only inexpensive and abundant (iron is the fourth most common element in the Earth's crust) but also environmentally benign.[3] Whilst there is no known biological role for palladium, iron has many roles in nature and for example, is found in haemoglobin, cytochrome P450, and the enzymes hydrogenase and nitrogenase (*Figure 1.01*). Consequently, there is a higher concentration of iron allowed in an active pharmaceutical ingredient (API) than palladium, although palladium is not necessarily toxic.[4]

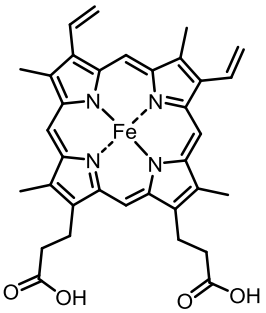


Figure 1.01. Iron-containing haem b in haemoglobin

1.1 Catalysis

In chemistry, palladium is best-known as a catalyst for hydrogenation,[5-6] oxidation[7] and cross-coupling reactions.[8] However, it was the development of palladium-catalysed cross-coupling reactions that firmly established it as a versatile and reliable catalyst, with Heck, Negishi and Suzuki being awarded the Nobel prize in chemistry in 2010 in recognition of their pioneering work on the subject.[9] Palladium- and nickel-catalysed cross-coupling reactions revolutionised carbon–carbon bond formation and they are now commonplace in countless syntheses.[10-11]

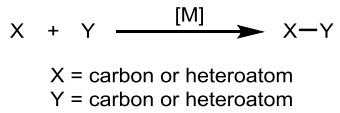
In comparison, iron-catalysed reactions have been considerably less well studied and

developed. Despite early applications of iron catalysis, for example the Haber-Bosch process uses a doped iron catalyst to synthesise ammonia from nitrogen and hydrogen from which 454 million tonnes of nitrogen fertiliser are produced every year,[12] the full potential of iron catalysis is only just being realised.[13-15]

Cross-coupling and hydrogenation are two reactions which demonstrate the development and increasing overlap of palladium and iron catalysis in both bond construction and functional group manipulation. Traditionally palladium catalysis has been used in cross-coupling and heterogeneous hydrogenation reactions but more recently iron catalysis has become a viable contender in the search for more sustainable catalysts and in some cases, the reactivity and selectivity achieved with iron has surpassed that of palladium.[13]

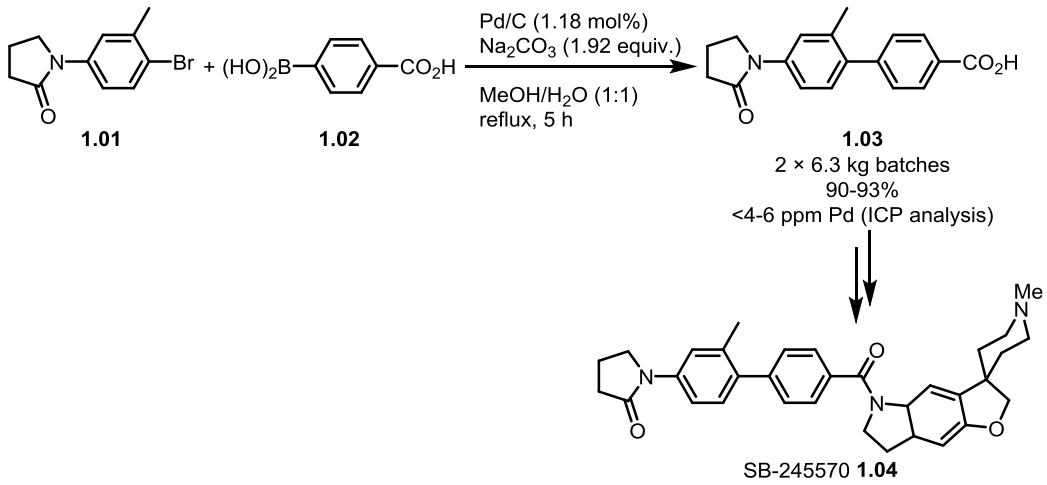
1.1.1 Cross-Coupling

Cross-coupling reactions can be defined as the formation of a carbon–carbon or carbon–heteroatom bond between two different partners, often catalysed by a transition metal (*Scheme 1.01*). Common transition metals used are palladium, copper and nickel.



Scheme 1.01. Cross-coupling reaction

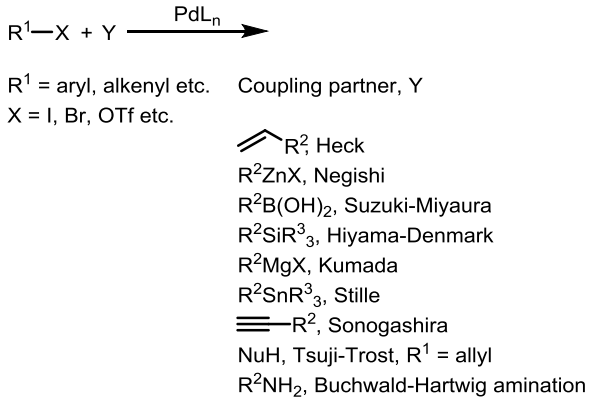
Cross-coupling reactions are now widely applied in the synthesis of natural products, pharmaceuticals, liquid crystals, and conjugated polymers, amongst other compounds of interests.[16] Suzuki-Miyaura coupling is the most widely used cross-coupling reaction in the syntheses of pharmaceuticals and one of the earliest industrial applications of the reaction was in the synthesis of SB-245570 **1.04**, a drug candidate for the treatment of depression (*Scheme 1.02*).[17] Excellent yields were consistently obtained with low catalyst loadings and 2 × 6.3 kg batches were prepared using this reaction, each containing negligible palladium residue.



Scheme 1.02. Suzuki-Miyaura cross-coupling in the synthesis of antidepressant SB-245570 **1.04**

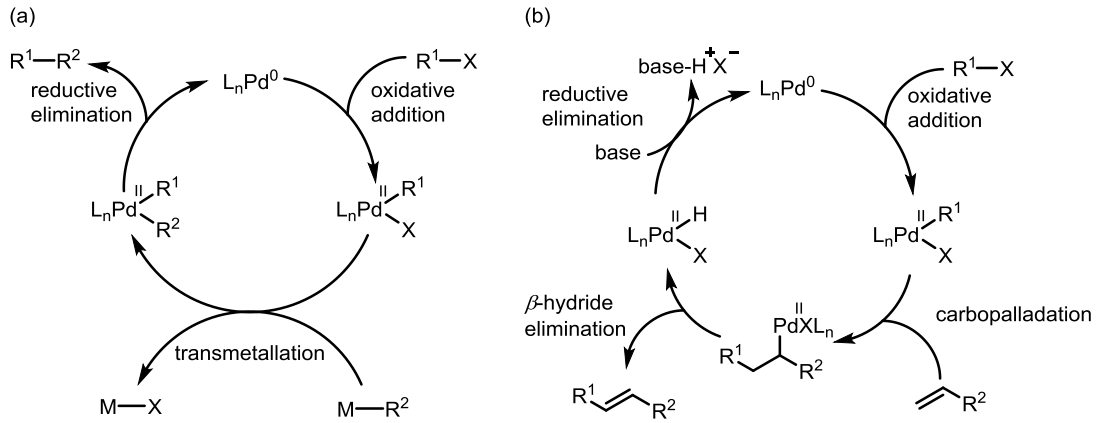
1.1.1.1 Palladium-Catalysed Cross-Coupling

In addition to the Heck, Negishi and Suzuki reactions, there are several other widely applied cross-coupling reactions, including the Sonogashira, Stille, Tsuji-Trost, Hiyama and Kumada, and the Buchwald-Hartwig amination for the formation of carbon–nitrogen bonds. All of these reactions use an organohalide (or equivalent) substrate but they differ in the second reagent (*Scheme 1.03*).[18]



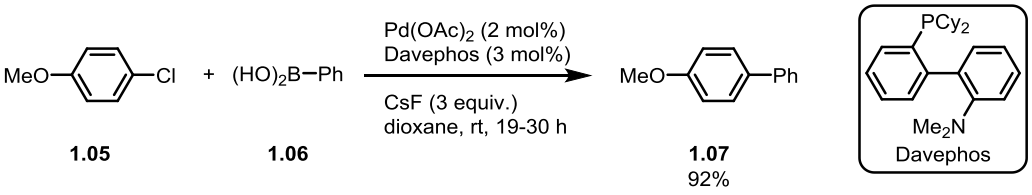
Scheme 1.03. Palladium-catalysed cross-coupling reactions

In general, the mechanism for cross-coupling involves oxidative addition, transmetallation and reductive elimination and the active catalyst is Pd(0) (either a Pd(0) catalyst is used directly or a Pd(II) precatalyst is used, which is most commonly reduced *in situ* with phosphine ligands) (*Scheme 1.04*).[19] For Heck reactions, which involve an alkene and not an organometallic as a coupling partner, transmetallation is replaced by carbopalladation and *β*-hydride elimination.



Scheme 1.04. (a) Standard mechanism for the palladium-catalysed cross-coupling of organohalides with organometallics and (b) Heck reaction

The Tsuji-Trost reaction and Buchwald-Hartwig amination allow the construction of carbon–heteroatom bonds, thus greatly expanding the scope of palladium-catalysed cross-coupling reactions. Recently, there has been an increase in the number of palladium-catalysed cross-coupling reactions using aryl chloride substrates.[20] Although the C–Cl bond is more chemically inert than the C–Br or C–I bond (experimental bond enthalpies DH_{298} PhCl: 97, PhBr: 84, PhI: 67 kcal mol^{-1})[21] aryl chlorides are less expensive and the commercially available compounds more diverse than the corresponding aryl bromides and iodides. The use of electron-rich phosphine and carbene ligands was found to be essential for reactivity. For example, in the first Suzuki-Miyaura cross-coupling of electron-rich aryl chlorides, 4-chloroanisole **1.05** underwent coupling with phenylboronic acid **1.06** in an excellent 92% yield using palladium acetate and phosphine ligand Davephos (*Scheme 1.05*).[22]



1.05 **1.06** **1.07** 92%

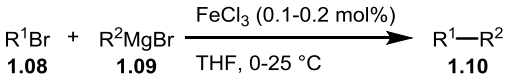
Scheme 1.05. Suzuki-Miyaura cross-coupling with an aryl chloride

The relative ease with which palladium can interconvert between Pd(0) and Pd(II), required for oxidative addition and reductive elimination, has undoubtedly contributed to the success of the metal as a catalyst in cross-coupling and other reactions. In comparison, alternative cross-coupling catalysts based on copper, nickel and iron, competitively undergo

one-electron redox reactions to generate carbon radicals, which have the potential to increase the number of byproducts formed. Nevertheless, there has recently been great interest in the use of these more sustainable metals for cross-coupling reactions.[23-27]

1.1.1.2 Iron-Catalysed Cross-Coupling

In the seminal report of iron-catalysed cross-coupling, which predates the corresponding palladium-catalysed reaction, Tamura and Kochi demonstrated that $FeCl_3$ could catalyse the coupling of alkenyl bromides **1.08** with Grignard reagents **1.09** to form alkene products **1.10** (*Table 1.01*);[28-29] the reaction is remarkably efficient with high yields being obtained using low catalyst loadings.



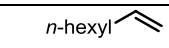
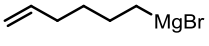
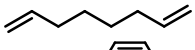
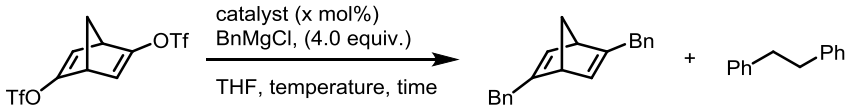
Entry	R^1Br	R^2MgBr	Product	Yield (%)
1		*n*-hexyl—MgBr	*n*-hexyl 	83
2				64
3	 *cis*/*trans* 70:30	*n*-hexyl—MgBr	*n*-hexyl  *cis*/*trans* 53:47	67

Table 1.01. First iron-catalysed cross-coupling reaction

Despite showing early promise, iron-catalysed cross-coupling remains underdeveloped and less well understood than the corresponding palladium-catalysed reaction. However, research has shown that in addition to the economic and environmental benefits of using iron, different reactivity is also possible. For example, high yields of diene ligand (*R,R)*-**1.12** were only obtained from bistriflate (*R,R*)-**1.11** using iron catalysis (*Table 1.02*).[30]



Entry	Catalyst (x mol%)	Temperature (°C)	Time (h)	(*R,R*)-1.12/1.13	Yield (%)
1	$NiCl_2$(dppe), 1	40	1	41:59	44
2	$PdCl_2$(dppf), 1	40	1	38:62	45
3	$Co(acac)_3$, 5[a]	0	0.25	38:62	28
4	$Fe(acac)_3$, 5[a]	0	0.25	93:7	98

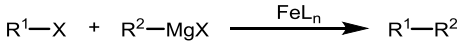
[a] NMP (1 equiv. with respect to BnMgCl) used as cosolvent

Table 1.02. Metal dependence of cross-coupling

With palladium and nickel the major product of the reaction was alkane **1.13**, resulting from

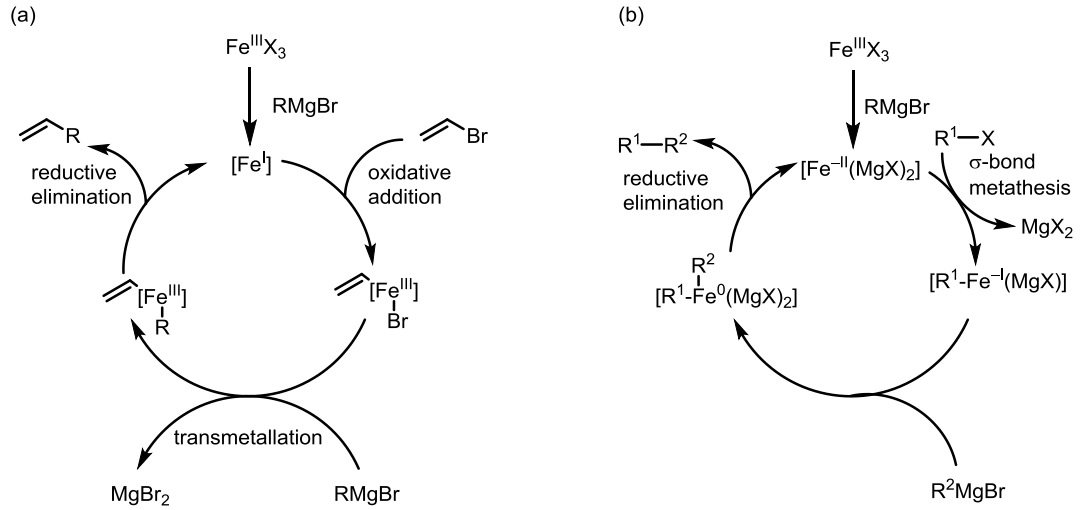
homocoupling of the Grignard reagent. Whilst the ligand and loading of the catalyst may also have played a part in the reaction outcome, as a catalyst for cross-coupling reactions, iron clearly has potential.

Iron-catalysed cross-coupling reactions generally involve the coupling of an organohalide (or equivalent) with a Grignard reagent, although organozinc or organomanganese coupling partners have been used (*Scheme 1.06*).[31-32] The instability and sensitivity to air and moisture of the active iron catalyst has made characterisation and the determination of its exact oxidation state difficult. However, a range of oxidation states have been proposed.



Scheme 1.06. Iron-catalysed cross-coupling

Reduction of the iron precatalyst by the Grignard reagent is known to occur and in the initial report of iron-catalysed cross-coupling, Kochi suggested that the active iron catalyst is an Fe(I) species (although Fe(0) is also plausible). The resultant Fe(I)/Fe(III) cycle resembles that for palladium-catalysed cross-coupling and involves oxidative addition, transmetallation and reductive elimination (*Scheme 1.07 (a)*).[28] More recently, Norrby and co-workers have conducted extensive experimental and computational studies into iron-catalysed cross-coupling and their results support the operation of an Fe(I)/Fe(III) cycle.[33]

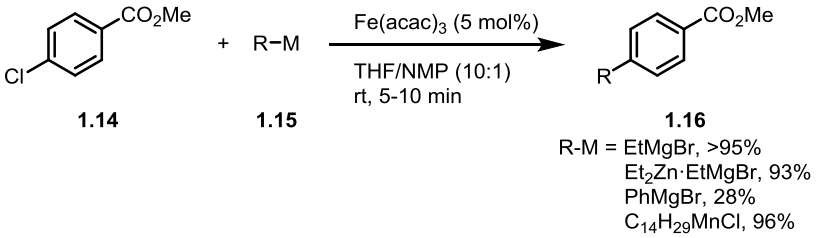


Scheme 1.07. Two-electron iron-catalysed cross-coupling mechanisms
(a) Original Fe(I)/Fe(III) mechanism proposed by Kochi and (b) Fe(−II)/Fe(0) mechanism proposed by Fürstner

Thirty years after Kochi's initial mechanistic hypothesis, Bogdanović and co-workers helped

revise the mechanism for iron-catalysed cross-coupling,[34-35] suggesting that the iron precatalyst first underwent a four-electron reduction to give the "inorganic Grignard reagent" $[Fe(MgX)_2]_n$ containing Fe(−II) (*Scheme 1.07 (b)*). Fürstner and Leitner then went on to suggest that σ-bond metathesis occurs to give $[R^1–Fe(MgX)]$, but owing to the absence of an iron-halide bond, transmetallation does not occur and instead alkylation of organoiron species $[R^1–Fe(MgX)]$ by the Grignard reagent leads to $[R^1R^2Fe(MgX)_2]$.[36] Reductive elimination then gives the cross-coupled product and returns the Fe(−II) iron species to the catalytic cycle. Significantly, this means that a formal Fe(−II)/Fe(0) catalytic cycle is operating. Whilst there is no direct evidence for this mechanism, related iron complexes, which are themselves able to catalyse cross-coupling reactions, have been isolated in which iron is in a formal oxidation state of Fe(−II) or Fe(0).[37-38] However, this mechanism only applies to EtMgX or higher alkyl Grignard reagents; for MeMgX and PhMgX that are unable to undergo *β*-hydride elimination, Fürstner *et al*. have proposed the existence of organoferrate complexes such as $[(Me_4Fe)(MeLi)][Li(OEt_2)]_2$. These complexes are prepared from exhaustive alkylation of the iron centre and are only able to catalyse the cross-coupling of highly activated substrates such as acid chlorides and enol triflates.

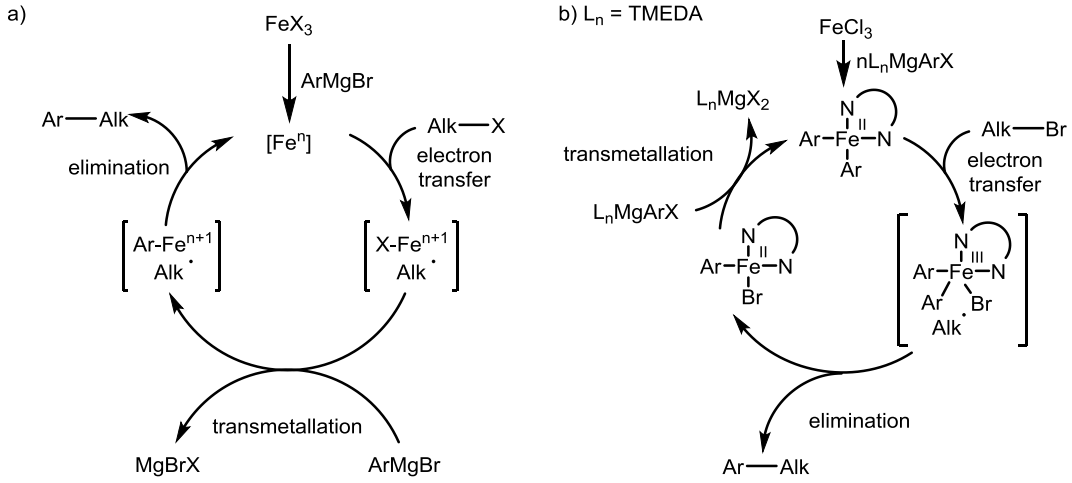
A representative example of iron-catalysed cross-coupling is the coupling of aryl chloride **1.14** with organomagnesium, -zinc and -manganese nucleophiles in excellent yield (with the exception of phenylmagnesium bromide) (*Scheme 1.08*).[39] In contrast, aryl bromides and iodides did not undergo cross-coupling and instead underwent protodehalogenation, owing to the highly reducing nature of the active iron catalyst.



Scheme 1.08. Iron-catalysed cross-coupling of aryl chloride **1.14** with different nucleophiles

In addition to mechanisms based on two-electron redox processes, radical mechanisms have

also been proposed (*Scheme 1.09*). Following generation of the active iron catalyst, Bedford *et al*. suggest a single-electron transfer occurs with the alkyl halide to give an alkyl radical/[$Fe^{n+1}X$] pair (*Scheme 1.09 (a)*).[40] Transmetallation with the aryl Grignard reagent then leads to an aryl iron complex, which undergoes elimination to release the cross-coupled product. Nakamura and co-workers have also proposed a single-electron transfer mechanism, specifically for the iron-catalysed cross-coupling between aryl Grignard reagents and alkyl halides with TMEDA as an additive (*Scheme 1.09 (b)*).[41] However, the order of the reaction steps differs to that suggested by Bedford.



Scheme 1.09. One-electron iron-catalysed cross-coupling mechanisms proposed by a) Bedford and b) Nakamura

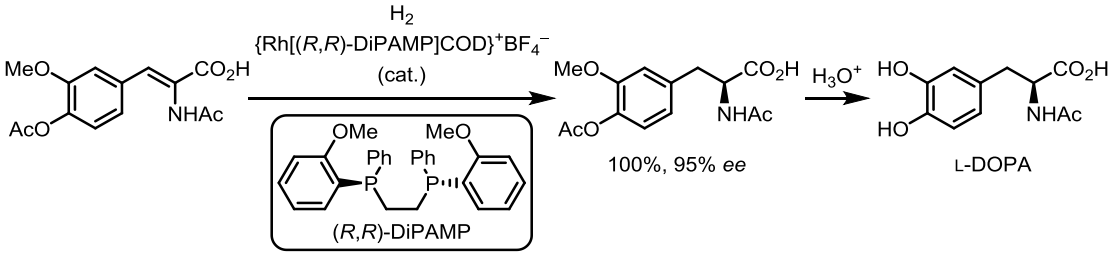
Overall, the mechanism for iron-catalysed cross-coupling remains controversial and it has been suggested that more than one catalytic cycle may be operating at a time.[38] The nature of the coupling partners and ligands may influence which catalytic cycle is operating and, in addition to the mechanisms discussed above, several other variants have been proposed, including the involvement of iron nanoparticles.[42-45]

Directly comparing palladium and iron in cross-coupling reactions, palladium-catalysed reactions are better understood and the reaction scope more established. They are also relatively insensitive to air and moisture and are tolerant of a wider range of functional groups (including hydroxyl and carbonyl groups) compared to iron-catalysed reactions. At present, iron-catalysed cross-coupling reactions are mainly limited to Grignard reagents and

thus the reaction is intolerant of air, moisture, and acidic and electrophilic functionalities. However, iron has the potential to become a highly successful cross-coupling catalyst in the coming years, as has been demonstrated in the cross-coupling of traditionally challenging electrophiles such as aryl chlorides[36] and secondary alkyl halides.[40]

1.1.2 Hydrogenation

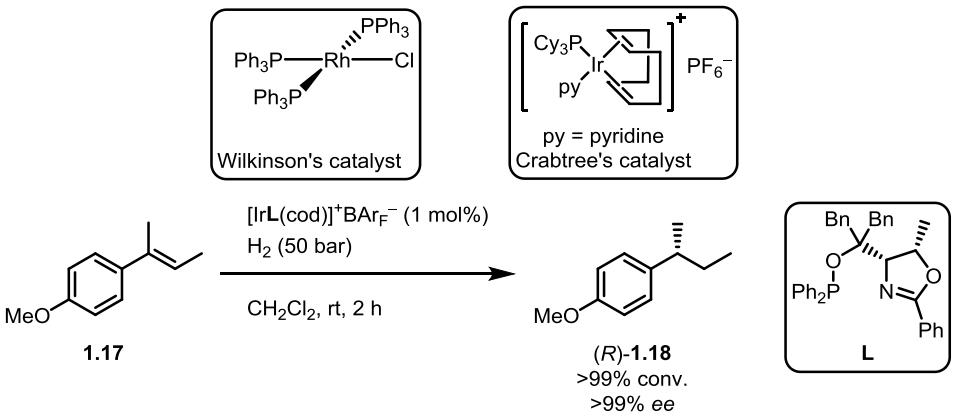
The value of being able to selectively reduce functional groups, such as alkenes, alkynes, aldehydes, ketones and imines, in both academic and industrial settings, cannot be understated. The Monsanto synthesis of L-DOPA, a drug used to treat Parkinson's disease, famously features an enantioselective hydrogen using an enantiopure rhodium catalyst (*Scheme 1.10*),[46] with Knowles and Noyori being awarded half the Nobel Prize in chemistry in 2001 for their work on catalytic asymmetric hydrogenation reactions.[47]



Scheme 1.10. Monsanto synthesis of L-DOPA

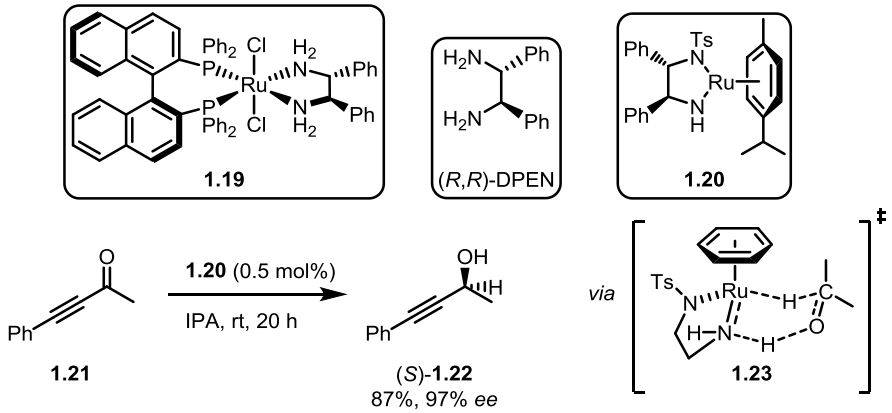
1.1.2.1 Precious Metal-Catalysed Hydrogenation

Typically, the homogenous reduction of functional groups has been achieved using precious metal catalysts, such as Wilkinson's rhodium catalyst $(Ph_3P)_3RhCl$[48] and Crabtree's iridium catalyst $[(COD)Ir(PCy_3)(py)]PF_6$[49] (COD = cyclooctadiene and py = pyridine) (*Scheme 1.11*). Crabtree's catalyst has since been modified with enantioenriched ligands to perform the asymmetric reduction of challenging substrates, for example unfunctionalised trisubstituted alkene **1.17**.[50-52]



Scheme 1.11. Common hydrogenation catalysts and an enantioselective hydrogenation by Pfaltz

Ruthenium-based catalysts have also been widely used for reduction owing to the inexpensive nature of ruthenium relative to other precious metals. Perhaps the most famous family of catalysts was developed by Noyori for the asymmetric hydrogenation (**1.19**)[53-54] and transfer hydrogenation (**1.20**)[55] (using *iso*-propanol or formic acid/triethylamine as a hydrogen donor) of ketones (*Scheme 1.12*). Hydrogenation using a hydrogen transfer reagent has been shown to be more useful, as this method negates the use of flammable hydrogen gas and pressure vessels. These catalysts are currently some of the most active and selective catalysts for the chemoselective reduction of ketones; for example, propargylic ketone **1.21** is reduced to alcohol **1.22** in an excellent 97% *ee* with transfer hydrogenation catalyst **1.20**.[56] Recent mechanistic studies have revealed asymmetric transfer hydrogenation proceeds *via* a nonclassical metal-ligand bifunctional mechanism involving ruthenium hydridoamido species **1.23** and a six-membered transition state.[57-59]

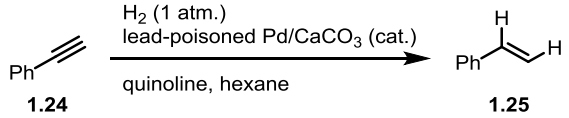


Scheme 1.12. Noyori's hydrogenation and transfer hydrogenation catalysts

Both palladium-catalysed hetero- (palladium metal on a support) and homogenous (soluble palladium complexes) reductions are also well established for the reduction of a variety of functional groups.[5-6, 60-61]

Heterogeneous systems have mainly been applied to three classes of substrate: alkenes and alkynes, carbonyl compounds, and nitrogen-containing multiple bonds. Whilst palladium can catalyse a wide range of reductions, other commonly used precious metals such as platinum, rhodium, ruthenium and nickel, are sometimes more effective.

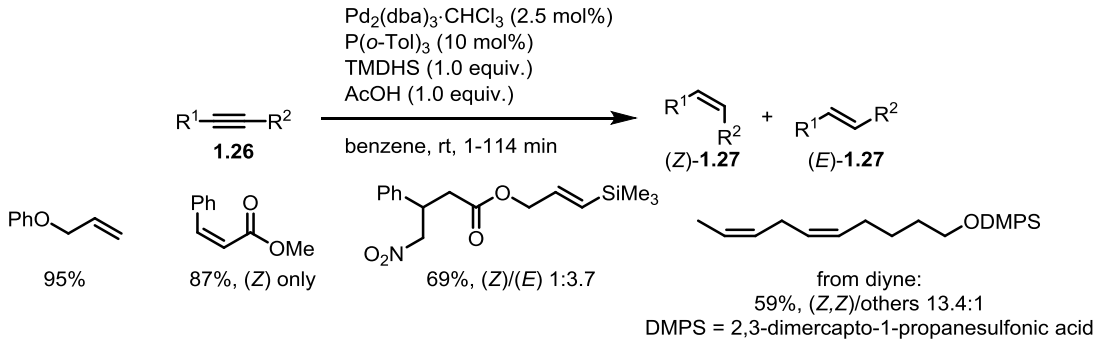
For heterogeneous catalysis, palladium is dispersed on a support such as activated carbon, alumina, silica and alkaline earth metal carbonates and sulphates. The reactivity of the catalyst can be modified through the addition of additives; for example, Lindlar's catalyst consists of lead-poisoned $Pd/CaCO_3$ and is used for the chemo- and stereoselective reduction of alkynes to *cis*-alkenes. In the reduction of phenylacetylene **1.24** to styrene **1.25**, quinoline is also added to further improve the selectivity of the reaction (*Scheme 1.13*).



1.24 **1.25**

Scheme 1.13. Palladium-catalysed reduction of phenylacetylene **1.24** to styrene **1.25**

Whilst homogeneous palladium-catalysed hydrogenation is unsuited to the reduction of alkenes, it has been shown to effectively catalyse the reduction of alkynes to alkenes, with the first example being reported in 1989 using tetramethyldihydrosiloxane (TMDHS) as a hydrogen donor (*Scheme 1.14*).[62] In general, alkynes **1.26** were reduced to *cis*-alkenes **1.27**. Notably, alkynes in conjugation with an ester could be selectively reduced and nitro groups, which can be reduced using heterogeneous palladium catalysis, remained intact.

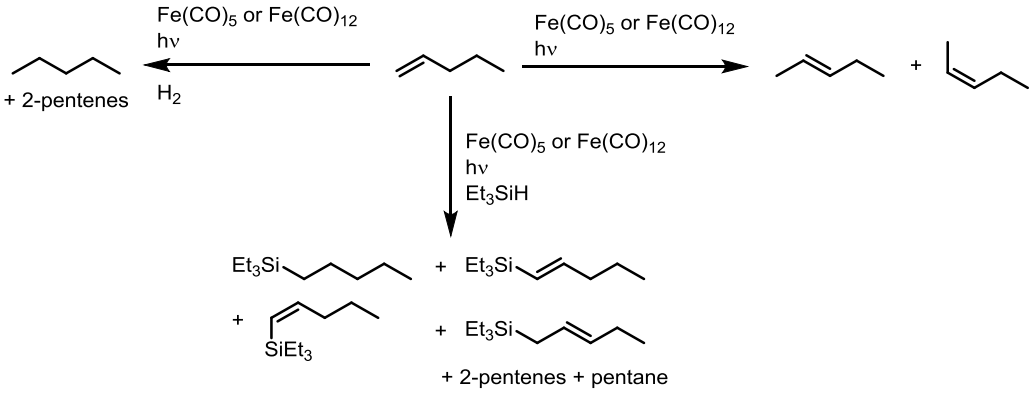


Scheme 1.14. First homogenous palladium-catalysed reduction of alkynes

Recently, owing to sustainability issues and potential novel reactivity, iron is being increasingly valued as an alternative reduction catalyst.[63]

1.1.2.2 Iron-catalysed Hydrogenation

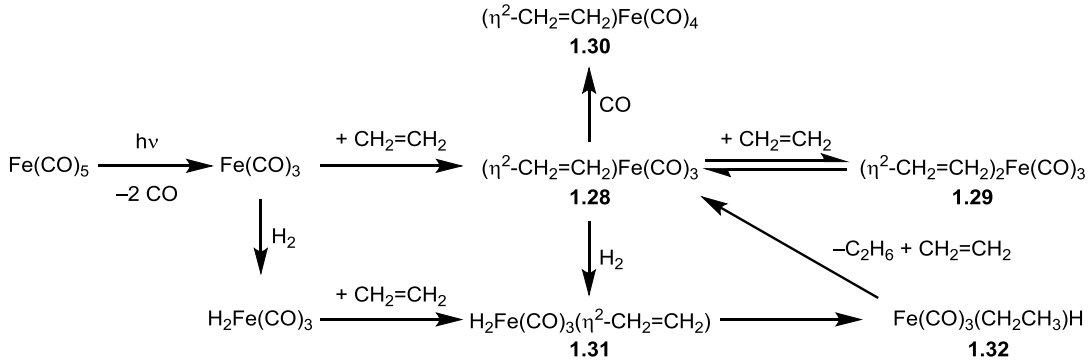
Early iron-catalysed reduction focused on the isomerisation, hydrogenation and hydrosilylation of alkenes using iron carbonyl compounds (*Scheme 1.15*).[64-65] The active catalyst in these reactions was proposed to be $Fe(CO)_3$, accessible from $Fe(CO)_5$ and $Fe_3(CO)_{12}$ by UV irradiation.



Scheme 1.15. Iron carbonyl compounds as early reduction catalysts

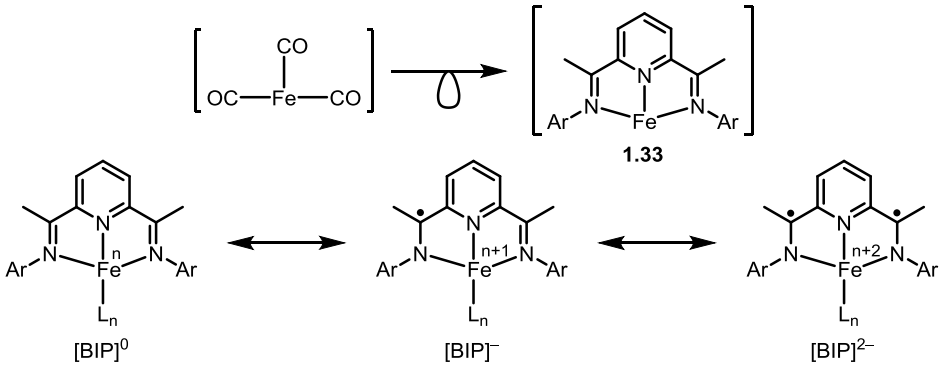
Following these seminal reports, Grant and co-workers conducted mechanistic studies into the gas-phase hydrogenation of ethylene and proposed $(\eta^2\text{-}CH_2{=}CH_2)Fe(CO)_3$ **1.28** to be the active catalytic species (*Scheme 1.16*).[66-68] Coordination of a second molecule of ethylene would lead to the resting state $(\eta^2\text{-}CH_2{=}CH_2)_2Fe(CO)_3$ **1.29** and coordination of an additional carbon monoxide ligand would be a deactivation pathway leading to the inactive $(\eta^2\text{-}CH_2{=}CH_2)Fe(CO)_4$ **1.30**. Therefore, the only productive pathway would involve coordination of hydrogen to give $H_2(\eta^2\text{-}CH_2{=}CH_2)Fe(CO)_3$ **1.31**, which can undergo

hydroferration (**1.32**) and reductive elimination to release ethane and the active catalyst.



Scheme 1.16. General mechanism for the hydrogenation of alkenes with iron carbonyl complexes

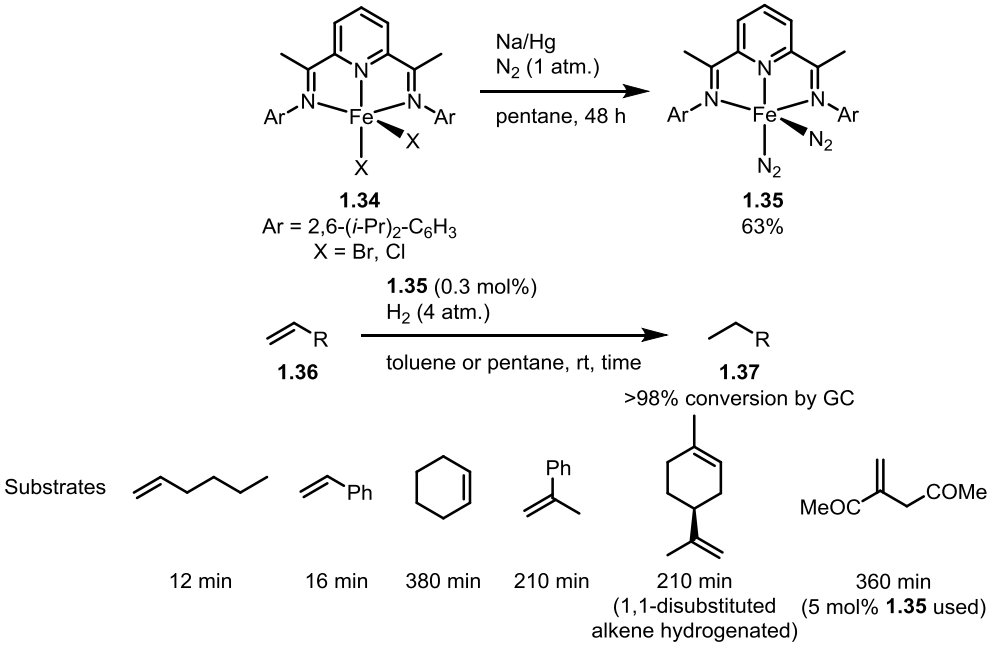
Interest in iron-catalysed reduction waned in the following years and it is only recently that this area has been reinvestigated. Inspired by the early iron-catalysed reductions, Chirik and co-workers designed iron bis(imino)pyridine complexes **1.33**, which are isolobal with $Fe(CO)_3$ (the proposed active catalyst in reductions using iron carbonyl compounds) (*Scheme 1.17*).[69] The choice of bis(imino)pyridine (BIP) as a ligand was twofold; iron bis(imino)pyridine complexes has precedence in catalytic carbon–carbon bond forming reactions[70-72] and bis(imino)pyridine is classed as a non-innocent ligand and can accept between one and three electrons.[73-76] It was hoped that this ability to accept electron density would enable iron to undergo the two-electron redox changes required (e.g. oxidative addition, reductive elimination) and suppress any side reactions arising from one-electron redox changes.



Scheme 1.17. Isolobal relationship between $Fe(CO)_3$ and iron bis(imino)pyridine complex 1.33, and redox activity of complex

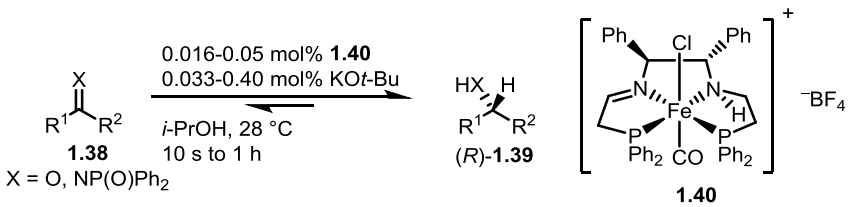
The formally Fe(0) complex **1.35** was prepared by the sodium-amalgam reduction of

iron(II) bis(imino)pyridine dibromide or chloride **1.34** under a nitrogen atmosphere (*Scheme 1.18*).[69] Although Fe(0) complex **1.35** is highly air and moisture sensitive,[77] it nevertheless successfully catalysed the hydrogenation of a range of unfunctionalised and electron-deficient olefins **1.36** at low catalysts loadings. Through deuterium labelling studies, it was shown that both deuterium atoms were delivered to the same face of the alkene, consistent with *syn*-hydrogenation.



Scheme 1.18. Synthesis of iron(0) bis(imino)pyridine complex **1.35** and application in the hydrogenation of olefins

Iron catalysts have also been used successfully for the hydrogenation of polar functionalities. The current state-of-the-art catalysts for the asymmetric hydrogenation of carbonyls are the iron amine(imine)bisphosphine complexes **1.40**, developed by Morris and co-workers (*Table 1.03*).[78] Using *iso*-propanol as a hydrogen source, a range of aldehydes, ketones and imines **1.38** underwent transfer hydrogenation to the corresponding enantioenriched alcohols and amines **1.39**. Remarkably high turnover frequencies (TOF) were observed with some substrates, for example, 119 s^{-1} at 50% conversion with acetophenone (*Table 1.03, entry 1*). In contrast, with $RuCl_2$((*R*)-tol-binap)[(*R*,*R*)-DPEN] (Noyori's hydrogenation precatalyst), acetophenone underwent hydrogenation (at 45 atm., 30 °C and in basic *iso*-propanol) to (*S*)-1-phenylethanol in 80% *ee* and at a TOF of 63 s^{-1}.[79]



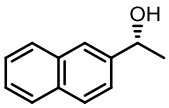
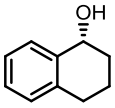
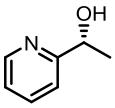
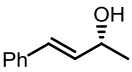
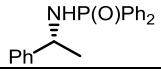
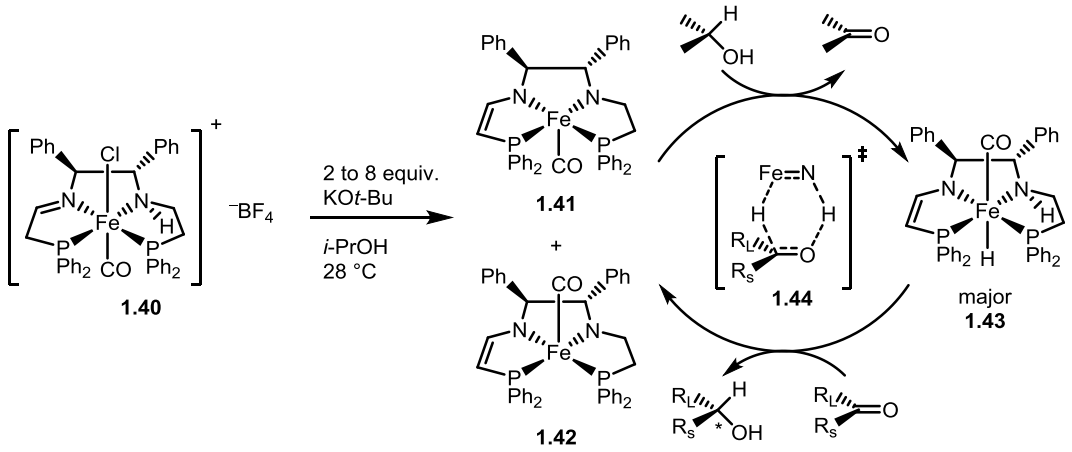
Entry	Product	Time to equilibrium	Yield (%)	TOF at 50% conv. (s^{-1})	*ee* at equilibrium (at 10 s)
1		180 s	82	119	78 (88)
2		180 s	84	158	83 (92)
2		1 h	73	4	33 (34)
4		10 min	88	38	-
5		1 h	67	3	54 (57)
6		6 min	98	100	24 (25)
7		25 s	99	242	-
8		4 min	55	14	40 (40)
9		20 s	100	10	>99 (>99)

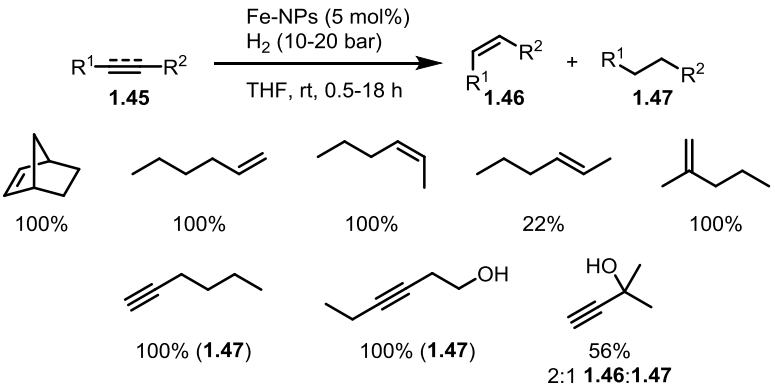
Table 1.03. Iron-catalysed transfer hydrogenation of ketones

The mechanism for the transfer hydrogenation is postulated to involve initial deprotonation of precatalyst **1.40** to form a mixture of isomers **1.41** and **1.42** (*Scheme 1.19*). These isomers can then formally accept a molecule of hydrogen from *iso*-propanol to give iron hydride complex **1.43** as the major isomer. The ketone substrate can then accept a hydride from iron hydride complex **1.43** by forming a hydrogen bond with the N–H functionality and orientating the large substituent towards the less bulky diamine side of the catalyst (**1.44**) to give enantioenriched alcohol.



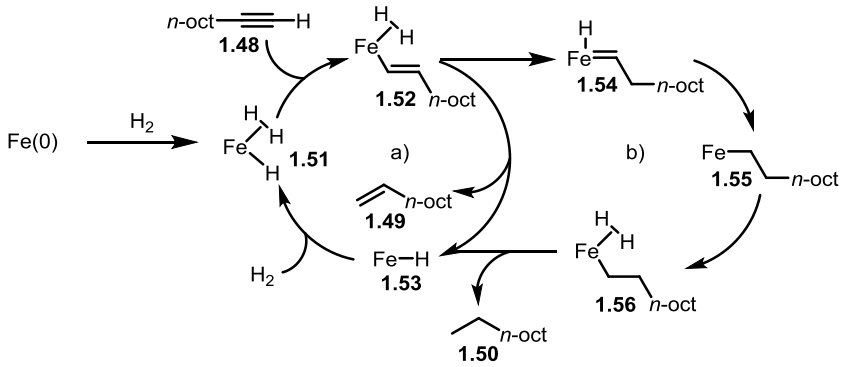
Scheme 1.19. Mechanism for transfer hydrogenation of ketone substrates catalysed by amine(imine)bisphosphine complex **1.40**

At the boundary between heterogeneous and homogeneous catalysis, de Vries and co-workers have recently demonstrated that Fe(0) nanoparticles are active for the reduction of terminal, 1,1- and 1,2-disubstituted alkenes and alkynes **1.45** (*Scheme 1.20*).[80-81] *Trans* alkenes were more challenging to hydrogenate than *cis* isomers and required higher temperatures to achieve full conversion, whilst tri- and tetrasubstituted alkenes did not undergo hydrogenation. The Fe(0) nanoparticles were generated from the reduction of iron salts with alkyl Grignard or alkyl lithium reagents according to a procedure previously developed by Bedford *et al*.[45]



Scheme 1.20. Hydrogenation of olefins catalysed by iron nanoparticles. Conversions shown

Based on kinetic experiments for the hydrogenation of 1-octyne **1.48**, a mechanism is proposed in which initially, octane **1.50** is not formed from the reduction of 1-octene **1.49**, but from rearrangement of alkenyl iron species **1.52** to alkylidene iron species **1.54** followed by hydrogenation (*Scheme 1.21*).



Scheme 1.21. Mechanism for hydrogenation of alkynes by Fe(0) nanoparticles

Although precious metal-catalysed hydrogenations are more robust, the recent progress in the field of iron-catalysed hydrogenation reveals that unprecedented activity and selectivity can be achieved with iron catalysis. As this field is still in its infancy compared to rhodium-, iridium- and palladium-catalysed hydrogenations, much more can be expected of iron catalysis and perhaps an increasing number of industrial syntheses will feature an iron-catalysed step in the coming years.

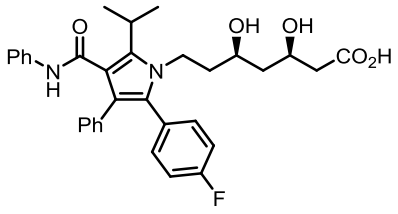
1.1.3 Novel Palladium and Iron-Catalysed Reactions

It was hoped that the unique properties of palladium and iron catalysis could be exploited to effect the construction of a variety of bonds in a controlled and selective manner. As exemplified in the cross-coupling and hydrogenation reactions discussed above, palladium and iron have been used as catalysts in a wide range of reactions, yet there remains untapped reactivity. In an age where sustainability is becoming of increasing importance, attention is turning to iron catalysis. Three classes of reaction were explored, namely asymmetric fluorination, C–H functionalisation and hydrofunctionalisation. For each of these reactions, a key aim was the development of an operationally simple, general and reliable protocol.

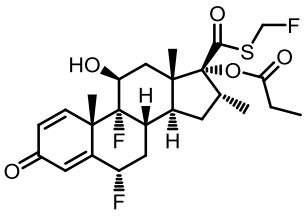
Chapter 2. Enantioselective Fluorination of Azaarylacetates and Amides

2.1 Introduction

Compared to the scarcity of fluorine-containing natural products, the number of fluorinated synthetic molecules is phenomenal; it is estimated that up to 35% of current agrochemicals and 20% of pharmaceuticals contain fluorine, including 4 of the top 10 best-selling drugs.[82] Lipitor and Advair Diskus are two of these drugs and contain aromatic and aliphatic fluorines respectively (*Figure 2.01*). Although the replacement of a hydrogen atom with a fluorine atom has a minimal steric effect on the compound (van der Waals radius of hydrogen: 1.2 Å; fluorine: 1.47 Å), it can have a profound beneficial effect on many of its other properties.[83] These include an electronic influence on neighbouring groups, improved lipophilicity, increased stability, and resistance to metabolic degradation, and as such fluorination has received considerable attention over the last decade.



Lipitor - inhibits cholesterol biosynthesis



Advair Diskus - anti-asthmatic

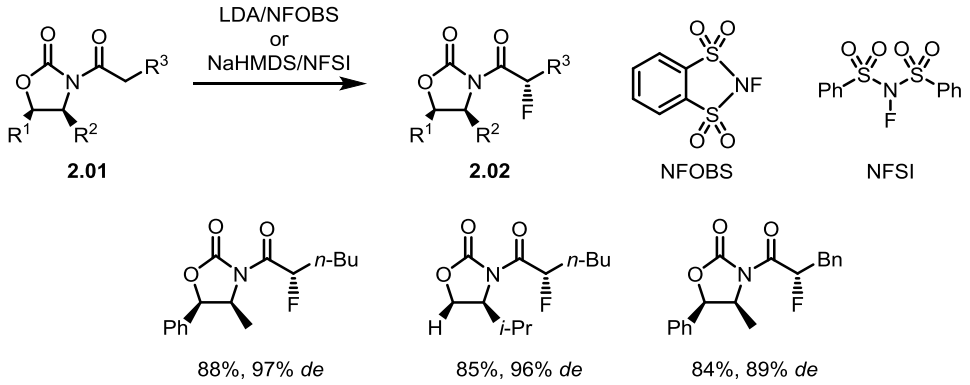
Figure 2.01. Examples of fluorinated best-selling drugs

Asymmetric fluorination is of particular importance in the pharmaceutical industry, as it is well known that stereoisomers behave differently within the chiral environment of a biological receptor.[84] For example, out of the three fluorines in Advair Diskus, two are attached to stereogenic centres and so their synthetic introduction must be carefully controlled.

2.1.1 Construction of Fluorinated Stereocentres

The generation of a fluorinated stereogenic centre can be achieved in two ways, either through the direct asymmetric introduction of fluorine (e.g. *via* a stereospecific S_N2 displacement at a pre-formed stereocentre), or through the conversion of prochiral

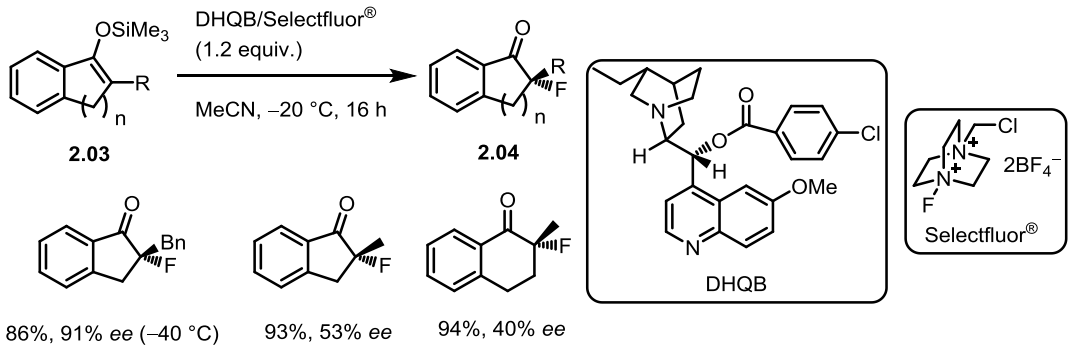
fluorinated substrates (where the fluorinated sp^2 centre is converted into an sp^3 stereocentre).[85] Asymmetric fluorination itself can be realised in two ways: through either substrate-controlled diastereoselective reactions, or reagent- or catalyst-controlled enantioselective reactions. In the first instance, an existing non-racemic stereocentre controls the stereoselectivity of the fluorination and a variety of chiral auxiliaries have fulfilled this role, including oxazolidinones,[86-88] 8-phenyl menthol,[89] and ephedrine.[90] Davis and co-workers showed that Evans's oxazolidinones could be used to prepare *α*-fluorinated imides **2.02** in excellent diastereoselectivity, based on the approach of *N*-fluoro-*o*-benzene-disulfonimide (NFOBS) or *N*-fluorobenzenesulfonimide (NFSI) from the less hindered *si* face of the imide enolate (*Scheme 2.01*).[86] Despite the high diastereoselectivities observed, removal of the chiral auxiliary sometimes proved problematic, as exposure to base resulted in racemisation of the stereocentre owing to the enhanced acidity of the *α*-fluoro proton in the product.



Scheme 2.01. Use of oxazolidinones in diastereoselective fluorinations

In the case of reagent- or catalyst-controlled enantioselective fluorinations, the substrate is exposed to a chiral fluorinating reagent, or a chiral catalyst in combination with an achiral fluorine source, respectively. Shibata and Cahard independently developed a series of chiral fluorinating agents based on cinchona alkaloids and Selectfluor® (transfer fluorination from Selectfluor® onto the cinchona alkaloids generates the *N*-fluoroammonium salts).[91-92] For example, the *N*-fluoroammonium salt of dihydroquinine-4-chlorobenzoate (DHQB) was used to prepare fluorinated indanones and tetralones **2.04** in up to 91% *ee* (*Scheme 2.02*).

However, this particular example uses stoichiometric cinchona alkaloid and it is only recently that catalytic versions of this reaction have been developed.[93]



Scheme 2.02. Use of cinchona alkaloids in reagent-controlled enantioselective fluorinations

Early work focussed on substrate-controlled diastereoselective reactions, but in recent years there has been growing interest in reagent- and catalyst-controlled enantioselective reactions and this can be further divided into nucleophilic and electrophilic fluorination. Out of nucleophilic and electrophilic fluorination, the latter has been the most exploited and hence electrophilic fluorination will form the main focus of this discussion.

2.1.2 Asymmetric Electrophilic Fluorination

Within the field of asymmetric electrophilic fluorination, a wide variety of methods have been used to install the fluorinated stereocentre in a broad range of substrates with high enantioselectivity (*Table 2.01*).[94-95]

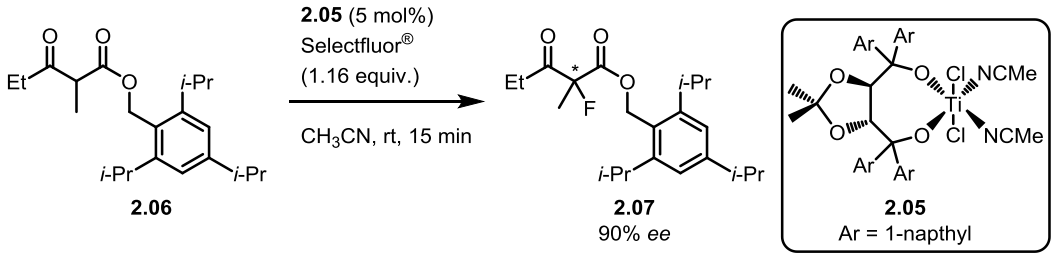
	Aldehydes	**Ketones**	**Esters**	**Lactones**	**Amides**	**Enoxysilanes**	**Enol acetates**	***β*-Ketoesters**	***β*-Ketoamides**	***β*-Ketophosphonates**	***α*-Amino nitriles**	***α*-Amino Esters**	***α*-Cyano Esters**	***α*-Nitro Esters**	**Oxindoles**	**Allylsilanes**	**Sulfones**
Chiral fluorinating agent	-	88	35	88	-	91	54	87	-	-	94	76	87	40	88	96	-
Transition-metal catalysis	-	-	99	-	88	-	-	99	99	98	-	-	99	-	96	-	99
Organocatalysis	99	36	-	-	-	-	-	70	-	-	-	-	76	-	-	-	-

Table 2.01. Enantiomeric excesses reported for a variety of substrates using three different electrophilic fluorination methods; reproduced from a review by Cahard and co-workers[94]

Out of the three approaches explored, transition-metal catalysis is the one that is most consistently able to generate products in excellent enantiomeric excess, and as such this approach is considered in more detail in the following section.

2.1.2.1 Transition-Metal Catalysis

In 2000, Togni and co-workers reported the pioneering example of transition-metal catalysed asymmetric electrophilic fluorination; using titanium TADDOLate complex **2.05** and achiral fluorine source Selectfluor®, a variety of *β*-ketoesters were fluorinated in up to 90% *ee* (*Scheme 2.03*).[96]

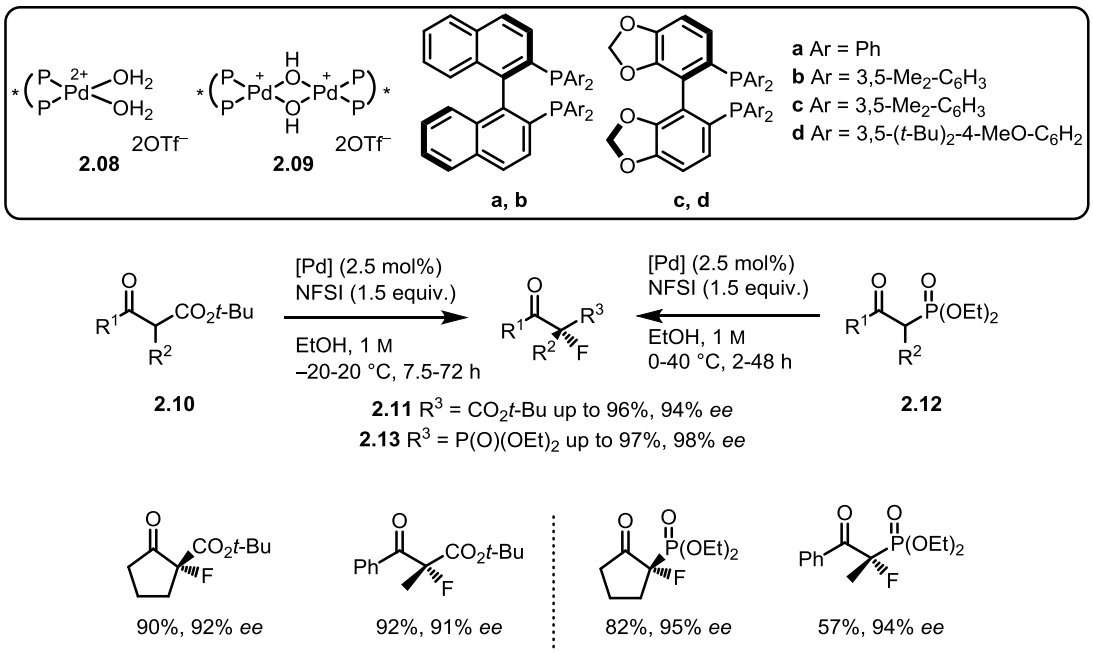


Scheme 2.03. First transition-metal catalysed asymmetric electrophilic fluorination

Although the *ee* was generally moderate with the exception of specific substrates e.g. **2.06**, the stage for transition-metal catalysis was set. In the years that followed numerous catalysts were developed and applied to a wide variety of substrates in which a chiral, non-racemic catalyst and an achiral fluorine source such as Selectfluor®, NFSI or *N*-fluoropyridinium salts were used. It is noteworthy that only those substrates containing a highly activated methine moiety have been successfully fluorinated, including *β*-ketoesters, *β*-ketophosphonates, *α*-cyanoacetates, *α*-cyanophosphonates and oxindoles.

2.1.2.1.1 Fluorination of *β*-Ketoesters and *β*-Ketophosphonates

In 2002, the Sodeoka group developed aqua and μ-hydroxo palladium bisphosphine complexes **2.08** and **2.09** that benefitted the field greatly in terms of both substrate scope and enantioselectivity (*Scheme 2.04*). These catalysts enabled the preparation of fluorinated *β*-ketoesters **2.11** in up to 94% *ee*,[97-98] *β*-ketophosphonates **2.13** in up to 98% *ee*,[98-99] and oxindoles in up to 96% *ee* (see *section 2.1.2.1.3*).[100]



Scheme 2.04. Fluorination using the Sodeoka group's state-of-the-art catalyst

Figure 2.02 depicts the proposed transition state for the fluorination of *β*-ketoester **2.10** with (*R*)-DM-BINAP palladium catalyst **2.08b** and explains the origin of the (*R*) enantioselectivity.[97] *β*-Ketoester **2.10** first forms a palladium enolate with catalyst **2.08b** to give complex **2.14**—the substrate binds to palladium through both oxygens in its 1,3-dicarbonyl motif to form a six-membered chelate. In the distorted square planar transition state, the ester *tert*-butyl moiety points away from the bulky phosphine aryl groups and this determines which enantiotopic face NFSI approaches. The ester *tert*-butyl moiety effectively shields the *si* face from NFSI and forces fluorination to occur on the sterically less hindered *re* face. Sodeoka states that phosphine phenyl groups were insufficiently bulky to force the *tert*-butyl group into a conformation capable of completely shielding the *si* face from fluorination and phosphine dimethyl or di(*tert*-butyl) substituted phenyl groups were essential for a high degree of enantiomeric excess in the product.

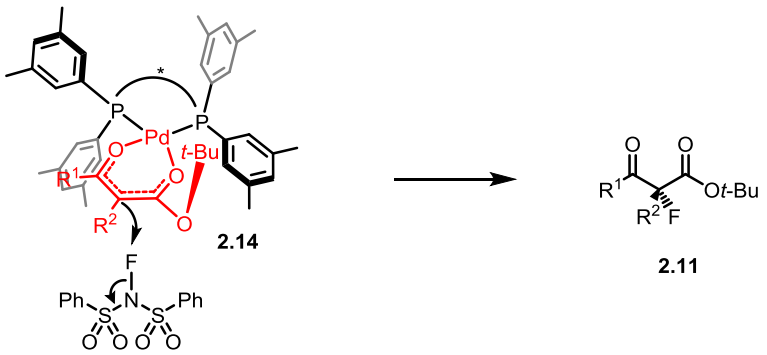
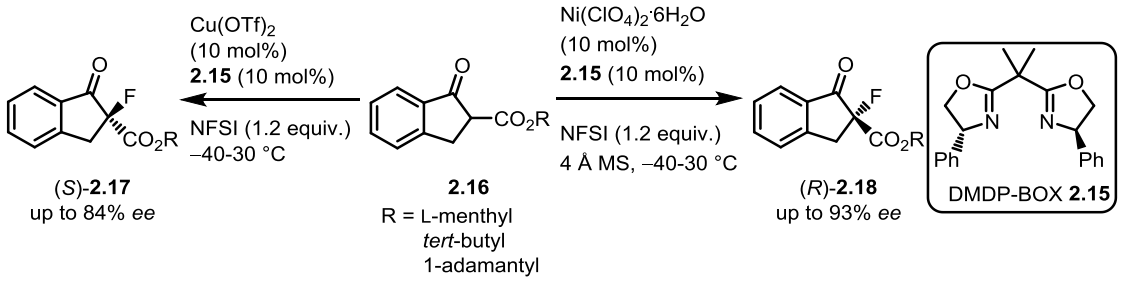


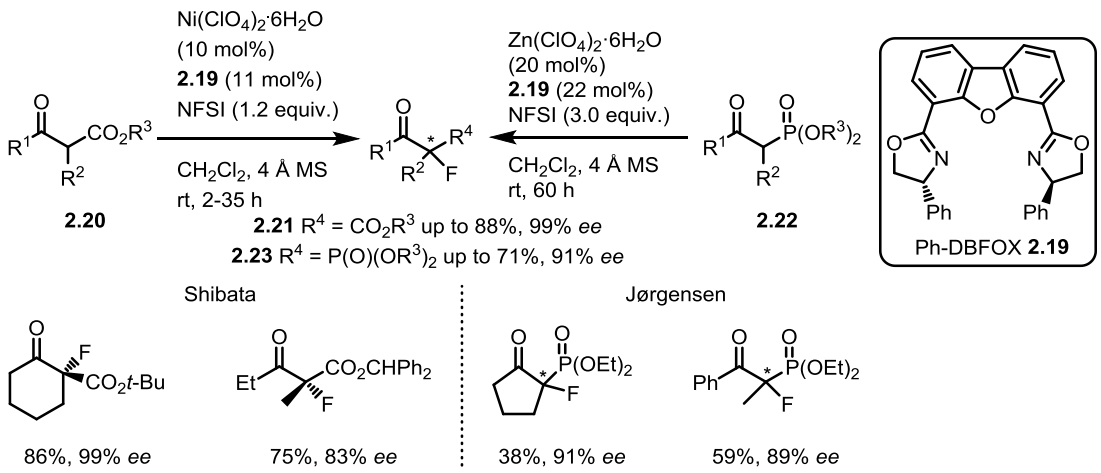
Figure 2.02. Sodeoka's proposed transition state for the fluorination of *β*-ketoesters

Bis(oxazolines) (BOX) **2.15** are a class of *N*,*N*-ligands that have been employed with a variety of metals to effect asymmetric enantioselective fluorination, with Shibata and co-workers demonstrating their broad scope in the development of an enantiodivergent route to fluorinated *β*-ketoesters **2.17** and **2.18** (*Scheme 2.05*).[101] They showed that the opposite configuration of the fluorinated stereocentre could be achieved using Ni(II)- and Cu(II)-dimethyldiphenylbis(oxazoline) (DMDP-BOX) complexes, as a result of the two different coordination geometries adopted by the complexes.



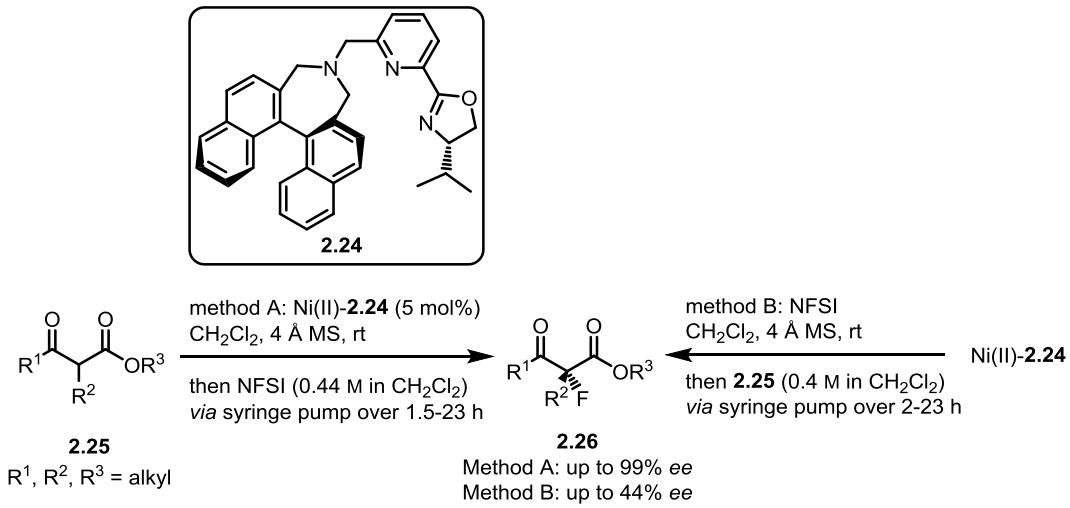
Scheme 2.05. Use of BOX ligands in asymmetric electrophilic fluorination

In 2005, Shibata and co-workers extended their methodology to include (dibenzofuran-4,6-diyl)-2,2'-bioxazoline (DBFOX) ligands, in the hope of improving upon the BOX system. It was shown that Ph-DBFOX **2.19** did provide better enantioinduction than DMDP-BOX **2.15**, and Ni(II)-Ph-DBFOX was used to prepare fluorinated *β*-ketoesters **2.21** and oxindoles in up to 99% *ee* (*Scheme 2.06*).[102] Simultaneously, Jørgensen and co-workers developed an analogous Zn(II)-Ph-DBFOX system to catalyse the fluorination of *β*-ketophosphonates **2.22** in up to 91% *ee* (the absolute configuration of the products was not given).[103]



Scheme 2.06. Use of DBFOX ligands in asymmetric electrophilic fluorination

During their research into the fluorination of *β*-ketoesters, Shibatomi and Iwasa showed that the order in which the reagents were added had a significant effect on the enantioselectivity of the reaction (*Scheme 2.07*).[104] They found that slow addition of NFSI to a solution of Ni(II)-**2.24** and substrate **2.25** (method A) gave product **2.26** in higher enantiomeric excess (up to 99% *ee*) than if all the reagents were added simultaneously (up to 94% *ee*).[105] Conversely when substrate **2.25** was added to a solution of Ni(II)-**2.24** and NFSI (method B), the *ee* of product **2.26** was substantially reduced (up to 44% *ee*).



Scheme 2.07. Effect of order of addition of reagents on enantioselectivity

With this in mind, Shibatomi and Iwasa proposed the existence of a second mechanistic pathway, in which the chiral metal complex activates NFSI—both NFSI and substrate

possess the requisite 1,3-dicarbonyl motif (*Figure 2.03*).[104, 106] The fluorinated *β*-ketoester will thus be formed in lower enantiomeric excess owing to the reduced influence of the catalyst—enantioinduction decreases with increasing distance between the reaction centre and source of chirality.

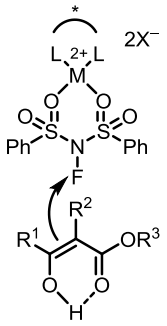
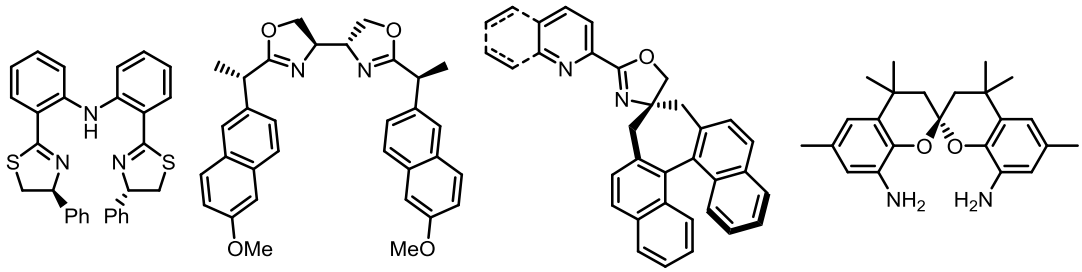


Figure 2.03. Proposed existence of second fluorination mechanistic pathway

Various *N,N*-ligands have also been used for the enantioselective fluorination of *β*-ketoesters, including bis(thiazoline) **2.27**, BOX **2.28**, spirooxazoline **2.29** and spirobichroman **2.30** (*Figure 2.04*).[107-110]



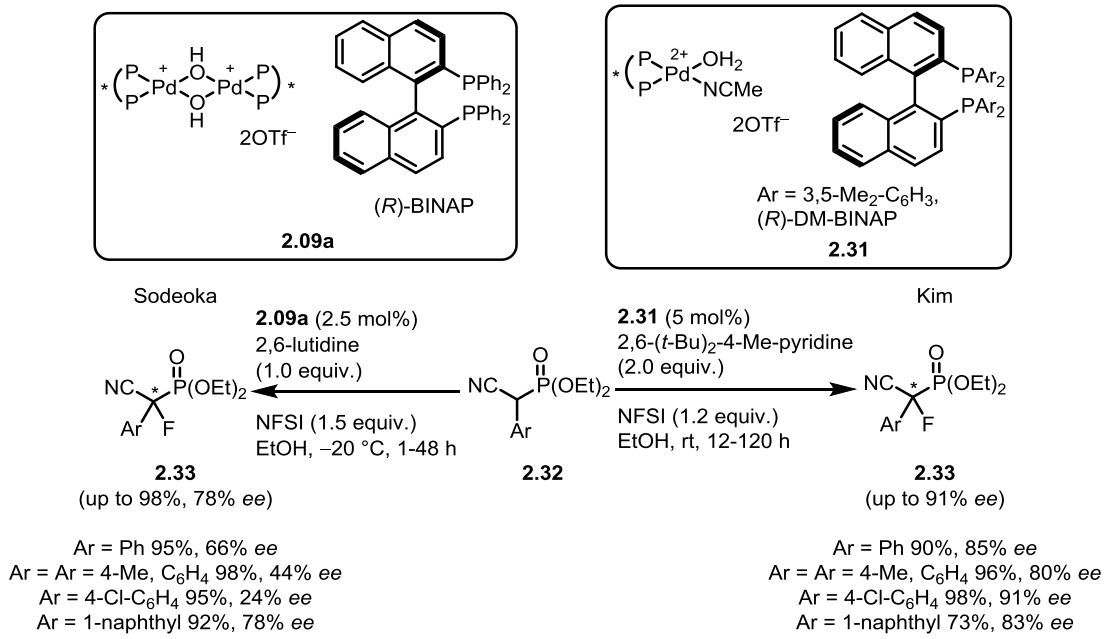
2.27 **2.28** **2.29** **2.30**

Figure 2.04. Alternative ligands for enantioselective electrophilic fluorination of *β*-ketoesters

2.1.2.1.2 Fluorination of *α*-Cyanophosphonates

In terms of substrate scope, Sodeoka and Kim raised the bar for asymmetric electrophilic fluorination in 2007, when they simultaneously reported the fluorination of *α*-cyanophosphonates **2.32** (*Scheme 2.08*).[111-113] Both groups made the observation that *α*-cyanophosphonates were a substantially less reactive class of substrates than *β*-ketoesters and *β*-ketophosphonates, and an external base was required to assist formation of the enolate. Nevertheless, Sodeoka successfully isolated fluorinated *α*-cyanophosphonates in up to 78% *ee*, and Kim in up to 91% *ee*. In addition to the lower reactivity of *α*-cyanophosphonates, only *α*-aryl substituted substrates underwent successful fluorination; *α*-alkyl substituted

substrates were unreactive. The absolute configuration of the products was not given.



Scheme 2.08. Enantioselective fluorination of *α*-cyanophosphonates

α-Cyanophosphonates cannot bind in the same way to the catalyst as *β*-ketoesters owing to the absence of the 1,3-dicarbonyl motif. Two modes of catalyst-substrate binding can be envisaged, either invoking the lone pair of the cyano nitrogen (**2.34**, monodentate binding), or a lone pair on the P=O oxygen in addition to the π-bond of the nitrile functionality (**2.35**, bidentate binding) (*Figure 2.05*).

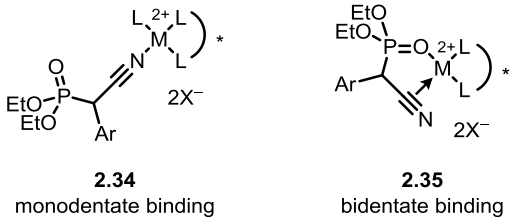


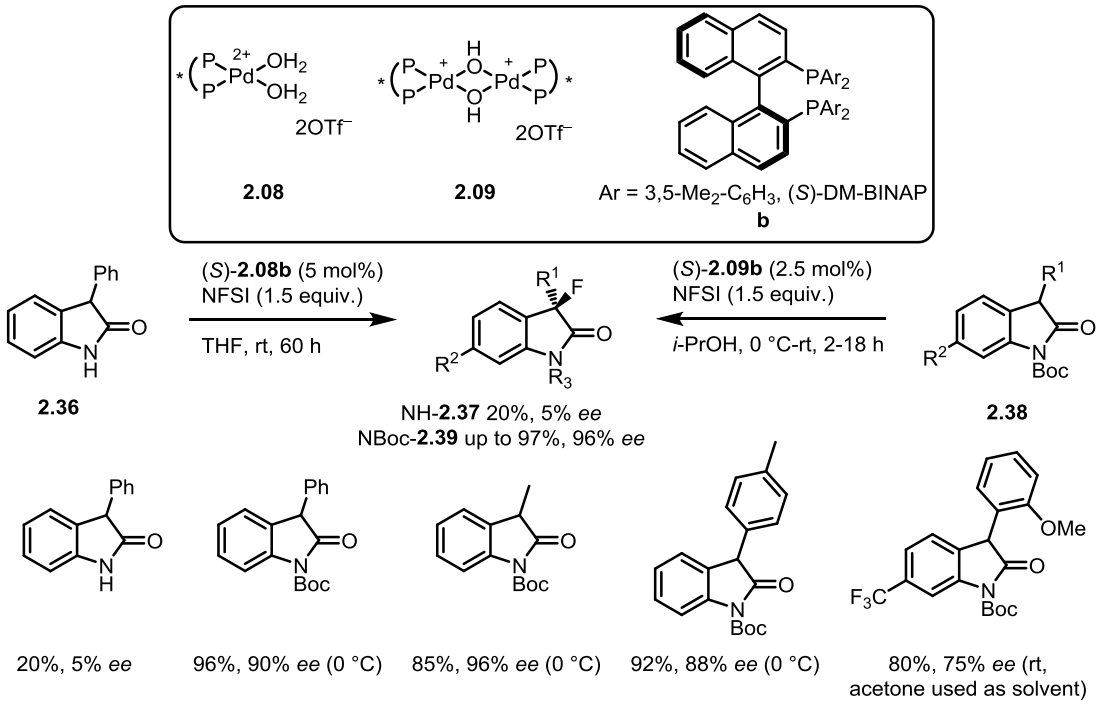
Figure 2.05. Proposed catalyst binding for *α*-cyanophosphonates

In the following years, *α*-cyanoacetates and -sulfones have also proven viable fluorination substrates and enantiomeric excesses as high as 93% and 99% have been achieved respectively.[114-115]

2.1.2.1.3 Fluorination of Oxindoles and Ketones

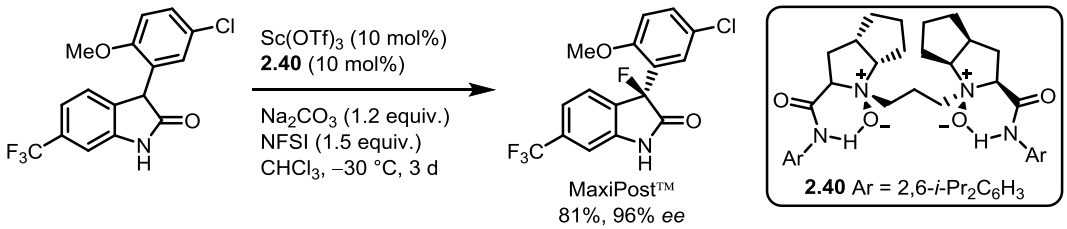
All of the substrates discussed so far have contained a methine group activated by two flanking electron-withdrawing groups. The fluorination of substrates in which a methylene

group is activated by only one electron-withdrawing group has also been well documented. However, a second coordinating group is usually required elsewhere in the molecule to facilitate bidentate binding of the catalyst. This was apparent during investigations into the fluorination of oxindoles by Sodeoka and co-workers (*Scheme 2.09*).[100] Unprotected oxindole **2.36** was poorly reactive towards fluorination, whereas Boc-protected oxindole **2.38** gave intended product **2.39** in good to excellent enantioselectivity. However, the lower reactivity observed for unprotected oxindole **2.36** compared to Boc-protected oxindole **2.38** could also be as a result of the lower acidity of the α-proton.



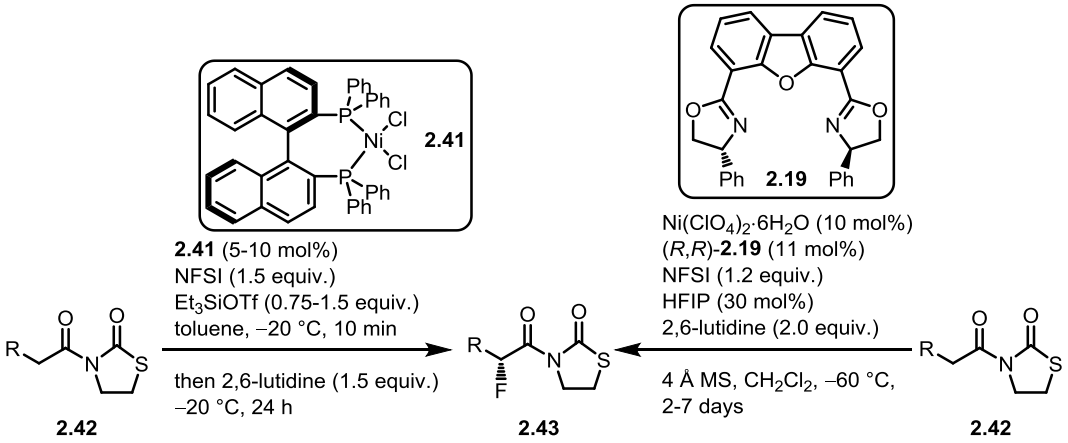
Scheme 2.09. Fluorination of unprotected and Boc-protected oxindoles

A catalyst system compatible with unprotected oxindoles was subsequently developed and applied in the highly enantioselective synthesis of MaxiPost™, a potassium channel opener (*Scheme 2.10*).[116]



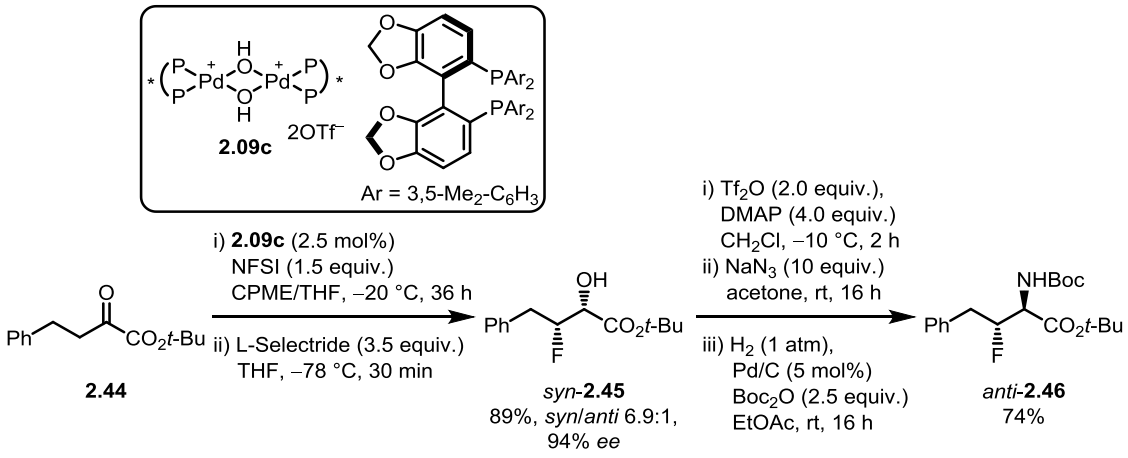
Scheme 2.10. Synthesis of MaxiPost™ involving fluorination of an unprotected oxindole

Similar fluorinations have since been performed on ketones. Thiazolidin-2-one derivatives **2.42** were successfully fluorinated by Sodeoka and co-workers in up to 88% *ee* (using a Ni(II)-(*R*)-BINAP catalyst),[117] and Shibata and Toru in up to 98% *ee* (using their Ni(II)-Ph-DBFOX system, *Scheme 2.11*).[118-119]



Scheme 2.11. Enantioselective fluorination of thiazolidin-2-one derivatives

Sodeoka showed that *α*-ketoesters **2.44** could also engage in bidentate binding with the catalyst (forming a five-membered chelate as opposed to the previously explored six-membered chelate) to give rise to fluorinated products **2.45** in up to 95% *ee* (*Scheme 2.12*).[120] Alcohol **2.45** was subsequently converted to *α*-fluoroamine **2.46** in three steps.



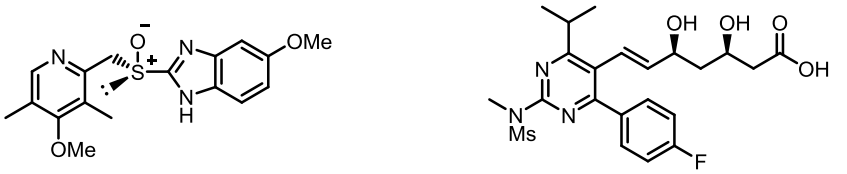
Scheme 2.12. Enantioselective fluorination of *α*-ketoesters

It is noteworthy that in the two previous examples (*Scheme 2.11 and 2.12*), the methylene group of the substrate was unsubstituted and only monofluorination was observed with no

erosion of enantiomeric excess, owing to the lower acidity of the α-fluoro proton in these systems in comparison to 1,3-dicarbonyl compounds.

2.1.3 2-Fluoroazaarylacetates and Amides

At present, the majority of asymmetric electrophilic fluorinations have been performed on 1,3-dicarbonyl containing substrates and it was envisaged that other activating groups, specifically a C=N functionality, could be used in place of a carbonyl group. Keeping within the framework of biologically active compounds, it was hoped to utilise a C=N functionality within a nitrogen-containing heterocycle, as these are prevalent structures in a wide variety of natural products and pharmaceuticals. In 2010, 18 of the top 20 small molecule-drugs contained at least one nitrogen heterocycle.[121] Nexium contains both a pyridine ring and benzimidiazole functionality and Crestor is a good example of a drug that contains both a nitrogen heterocycle (pyrimidine) and a fluorinated moiety (*Figure 2.06*).



Nexium - antacid/stomach ulcers **Crestor** - inhibits cholesterol biosynthesis

Figure 2.06. Examples of top-selling drugs containing heterocycles

In addition to the desirable fluorinated and heterocyclic components of a drug, it is also important to retain flexibility to enable subsequent manipulation and facilitate the preparation of a series of analogues.

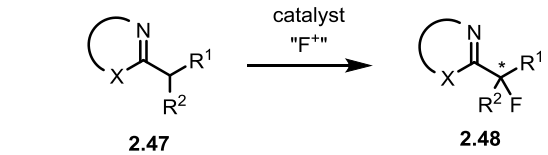
To this end, it was envisaged that the above methodology could be extended to the preparation of 2-fluoroazaarylacetates and amides (*Figure 2.07*), which contain a carbonyl functionality to provide a handle for further manipulation. Ultimately, it was hoped that these could act as useful building blocks for the preparation of therapeutic agents or other molecules of interest.

Figure 2.07. 2-Fluoroazaarylacetates and amides

2.2 Results and Discussion

2.2.1 Aims

Previous work in the Lam group has shown azaarenes to be capable activating groups in a variety of stereochemistry-generating reactions and it was anticipated that this might be extended to fluorination (*Scheme 2.13*). [122-123] A range of azaarenes could be prepared to explore the scope of fluorination, yet substrates containing a second activating group (R^1) might be requisite for fluorination based on literature precedent.[100]

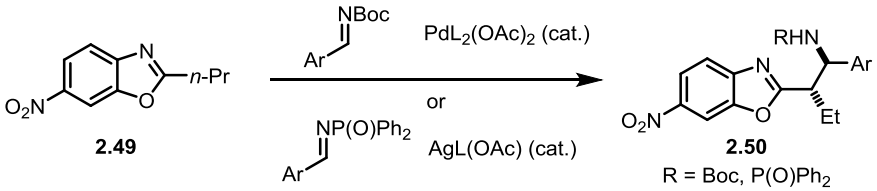


R^1 = alkyl, aryl, CO_2R, $CONR_2$
R^2 = alkyl, aryl

Scheme 2.13. Fluorination concept

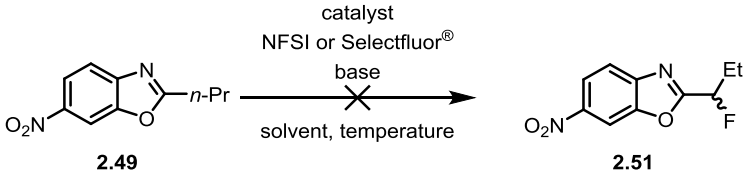
2.2.2 Initial Fluorinations

To test the viability of azaarenes in fluorination reactions, alkyl benzoxazole **2.49** was selected, owing to its success in a series of diastereoselective imine additions (*Scheme 2.14*).[124] Most importantly, benzoxazole **2.49** had shown that it could tautomerise to the enamine and that a transition-metal catalyst could control the stereochemistry of addition.



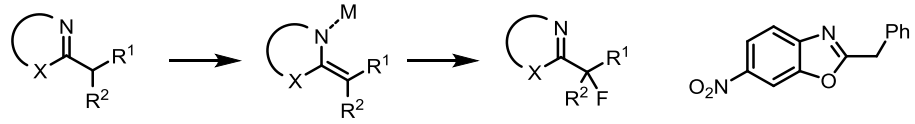
Scheme 2.14. Diastereoselective addition of azaarenes to imines

The fluorination of benzoxazole **2.49** was attempted with various catalysts, fluorine sources, basic additives, solvents and temperatures, but the crude ^1H NMR spectra from these reactions showed only starting material (*Scheme 2.15*).



Scheme 2.15. Initial fluorinations

It may be that benzoxazole **2.49** is insufficiently activated for fluorination. Since the mechanism for electrophilic fluorination would involve metal enamide **2.52** formation, it was hoped that an additional electron-withdrawing group would promote its formation (*Scheme 2.16*). Substrate **2.53** containing a phenyl group was chosen to test this hypothesis.



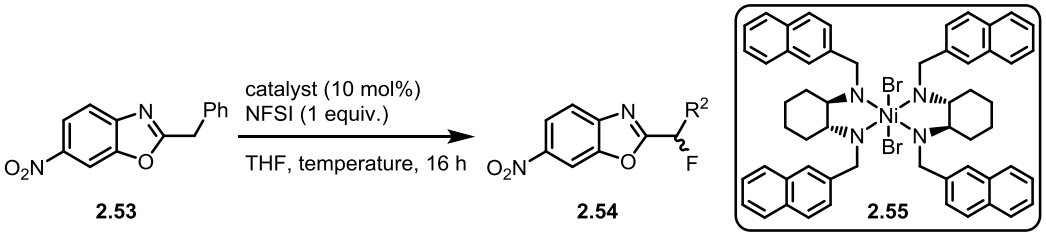
2.47 **2.52** **2.48** **2.53**

R^1 = alkyl, aryl, CO_2R, $CONR_2$

R^2 = alkyl, aryl

Scheme 2.16. Consideration of metal enamide intermediate **2.52**

We were pleased to observe fluorination of benzyl benzoxazole **2.53** with AgOAc, although the conversions were low and heating the reaction to 100 °C did not result in an increase in conversion (*Table 2.02*, *entries 1-3*). Catalyst **2.55**, which had been used successfully in the enantioselective Michael addition of azaarylacetates and amides to nitroalkenes,[125] was ineffective and no reaction occurred (*entry 4*). These observations suggested that two coordinating C=X functionalities were required for fluorination.



2.53 **2.54** **2.55**

Entry	Catalyst	Temperature	Conversion (%)[a]
1	AgOAc-2,2'-bipyridyl	rt	7%
2	AgOAc-(±)-BINAP	rt	3%
3	AgOAc-2,2'-bipyridyl	100 °C	4%
5	**2.55**	rt	no reaction

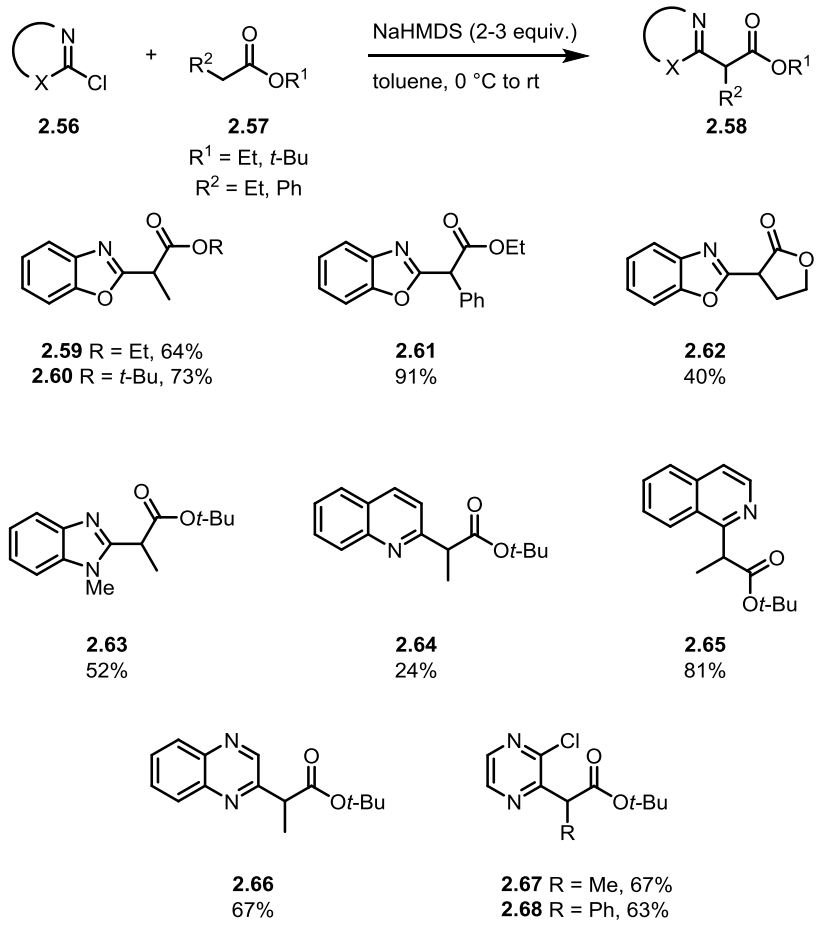
[a] conversion determined by ^{1}H NMR spectroscopy based on remaining substrate

Table 2.02. Initial results

2.2.3 Substrate Synthesis

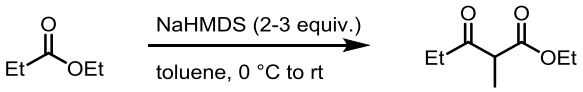
As opposed to amides, esters are more electrophilic and undergo functional group interconversions more readily. Therefore, we decided to concentrate on the synthesis and fluorination of azaarylacetates **2.58**, with a substituent at the 2-position to prevent either difluorination or racemisation of the monofluorinated product.

The majority of substrates **2.58** were prepared in one step through the reaction of readily available heterocyclic chlorides **2.56** with the enolates of simple esters **2.57**, using the methodology developed by Shen and co-workers (*Scheme 2.17*).[126] This allowed the preparation of a broad range of substrates **2.59-2.68**, including benzoxazoles, benzimidazoles, and various other azaarenes, in good yield.



Scheme 2.17. General procedure for the preparation of azaarylacetates

However, in general this methodology was limited to the preparation of *tert*-butyl esters from an appropriate heterocyclic chloride and *tert*-butyl propionate owing to a competing Claisen condensation when other esters were used e.g. with ethyl propionate (*Scheme 2.18*).

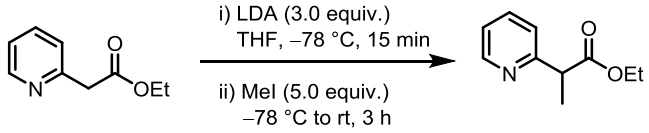


Scheme 2.18. Competing Claisen condensation for methyl and ethyl propionate

Nevertheless, substrates containing a broad range of functionalities were prepared using this strategy. Replacing the heterocyclic oxygen in benzoxazole **2.60** with nitrogen in

benzimidazole **2.63** would allow a direct comparison of the two azaarenes to be made. Quinoline **2.64** and isoquinoline **2.65** were designed to test the activating potential of a heterocyclic imine that is not in conjugation with another heteroatom. Furthermore these structural isomers would allow the position of the nitrogen in relation to the neighbouring aryl ring to be explored. Finally quinoxaline **2.66** and pyrazines **2.67** and **2.68** would probe the effect that an additional inductively stabilising heteroatom (**2.66**-**2.68**) and aryl ring (**2.66**) would have on activation and subsequent fluorination.

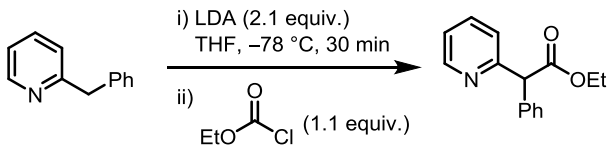
A variety of additional azaarylacetates were also prepared according to literature procedures. For example, pyridyl ester **2.70** was accessed through the methylation of commercially available ester **2.69** in 68% yield (*Scheme 2.19*).[127]



2.69 **2.70** 68%

Scheme 2.19. Synthesis of pyridyl ester **2.70**

Using an opposite strategy to the one used for the preparation of the majority of substrates (**2.59**-**2.68**), the preparation of pyridyl ester **2.72** involved the addition of the lithium enolate of 2-benzylpyridine **2.71** to ethyl chloroformate (with the azaarene acting as the nucleophilic synthon and the ester the electrophilic synthon) (*Scheme 2.20*). Pleasingly this alternative strategy worked well and pyridyl ester **2.72** was prepared in 76% yield. Pyridyl esters **2.70** and **2.72** are identical apart from the substituent at the 2-position, allowing the effect of the phenyl substituent on both the reactivity and the stereoselectivity of the fluorination reaction to be explored.

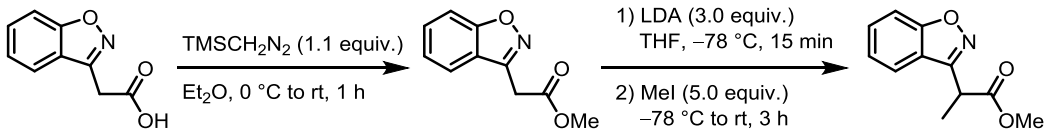


2.71 **2.72** 76%

Scheme 2.20. Synthesis of pyridyl ester **2.72**

Benzisoxazole **2.74** was isolated from the reaction of corresponding commercially available

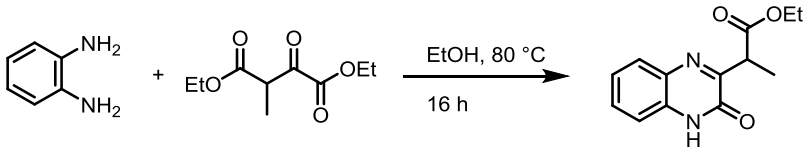
acid **2.73** with TMS diazomethane in 66% yield (*Scheme 2.21*), which was subsequently treated with LDA and methyl iodide to yield benzisoxazole acetate **2.75** in 36% yield. Careful monitoring of the methylation was required as intermediate **2.74** also underwent double methylation, reducing the yield.



2.73 **2.74** 66% **2.75** 36%

Scheme 2.21. Synthesis of benzisoxazole **2.75**

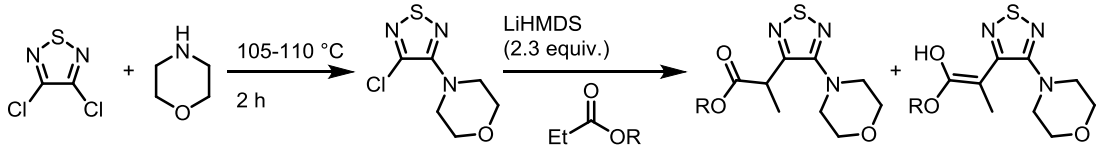
Quinoxaline derivative **2.78** was prepared from diamine **2.76** and diester **2.77** in refluxing ethanol in 76% yield (*Scheme 2.22*).[128]



2.76 **2.77** **2.78** 76%

Scheme 2.22. Synthesis of quinoxalinone **2.78**

The preparation of thiadiazole **2.81** enabled access to the literature known compounds thiadiazole esters **2.82** and **2.83** in both keto and enol forms (*Scheme 2.23*). Refluxing neat thiadiazole **2.79** with morpholine **2.80** gave morpholine thiadiazole **2.81** in 68% yield.[129] A divergent ester synthesis was then pursued: reaction with LiHMDS and ethyl propionate gave both keto and enol ethyl ester thiadiazole **2.82** in good yield, whilst with LiHMDS in combination with *tert*-butyl propionate, keto and enol *tert*-butyl ester **2.83** were isolated in very good yield.[130]



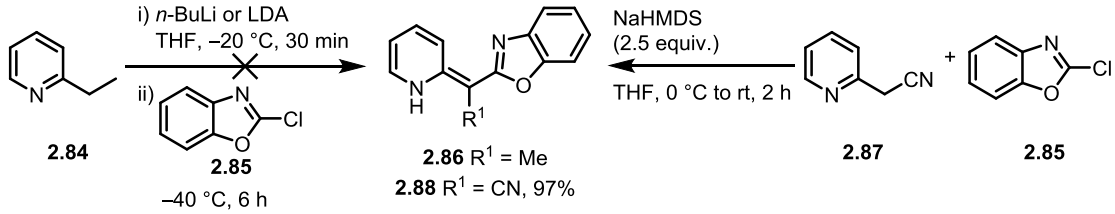
2.79 **2.80** **2.81** 68%

2.82 R = Et, 78% combined yield
2.83 R = *t*-Bu, 86% combined yield

Scheme 2.23. Synthesis of thiadiazoles **2.82** and **2.83**

As the main aim of the project focused on azaarenes as potential activating groups for

fluorination, substrates containing two azaarenes in a 1,3-relationship were also investigated. Pyridyl benzoxazole **2.86** was targeted, as substrates containing pyridine and benzoxazole heterocycles had already been synthesised (*Scheme 2.24*). Unfortunately, the reaction of the lithium enamide of 2-ethyl pyridine **2.84** with 2-chlorobenzoxazole **2.85** proved more difficult than expected, with a number of different conditions failing to yield any of the intended product. Eventually, the nitrile analogue (**2.88**) was prepared in excellent 97% yield. It is noteworthy that nitrile **2.88** existed purely in enamine form, identifiable in the ^{1}H NMR spectrum by the absence of an aliphatic CH peak and the presence of a broad NH singlet at 15.52 ppm.



Scheme 2.24. Pyridyl benzoxazole **2.88** synthesis

2.2.4 Initial Screening

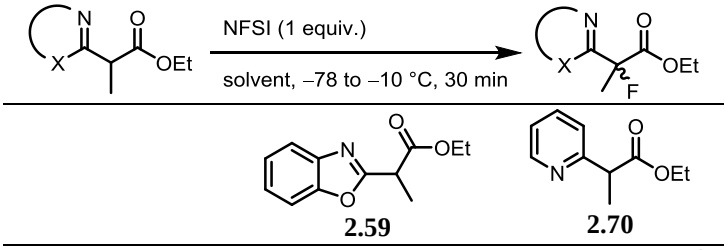
At this point, it was of the utmost importance to check for a background reaction that would give rise to racemic fluorinated products. If a background reaction was found to be occurring, then the stereoselectivity of an asymmetric fluorination would suffer under such conditions and any *ee* values obtained with an enantioenriched catalyst would not be a true reflection of the system.

2.2.4.1 Monitoring of Background Reaction

Esters **2.59** and **2.70** were treated with NFSI in THF at room temperature and a background reaction was observed for both substrates by TLC analysis. To suppress, or at the very least minimise this reaction, the temperature at which the background reaction occurred and the solvent which most suppressed the background reaction were investigated.

The reaction temperature was first investigated in ethanol, *iso*-propanol and acetonitrile—solvents commonly used for fluorination (*Table 2.03*).[97] No background reaction was

observed for substrates **2.59** and **2.70** in ethanol and *iso*-propanol at −10 °C after thirty minutes (*Table 2.03, entries 1 and 2*). In addition, only a negligible conversion was recorded in acetonitrile (*entry 3*).

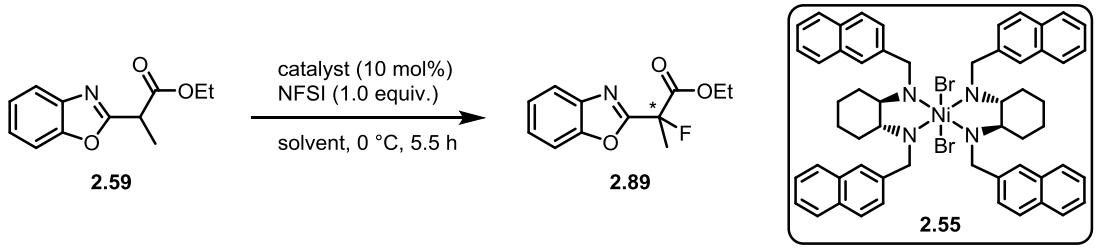


Entry	Solvent	Conversion (%)[a]	Conversion (%)[a]
1	EtOH	0	0
2	*i*-PrOH	0	0
3	MeCN	4	2

[a] conversion determined by ^{1}H NMR spectroscopy based on remaining substrate

Table 2.03. Monitoring of background reaction in different solvents

As the background reaction was determined to be inconsequential at –10 °C, it was decided for the sake of practicality to perform the solvent screen for ester **2.59** at 0 °C using an ice bath (*Table 2.04*). The solvent screen was conducted by measuring the % conversion of the uncatalysed and catalysed reaction and calculating the relative conversion.



Entry	Solvent	Conversion without 2.55 (%)[a]	Conversion with 2.55 (%)[a]	Relative conversion
1	EtOH	7	77	11
2	*i*-PrOH	0	50	-
3	MeCN	23	77	3.3
4	Et_2O	7	50	7.1
5	THF	9	83	9.2

[a] conversion determined by ^{1}H NMR spectroscopy based on remaining substrate

Table 2.04. Solvent screen for ester **2.59**

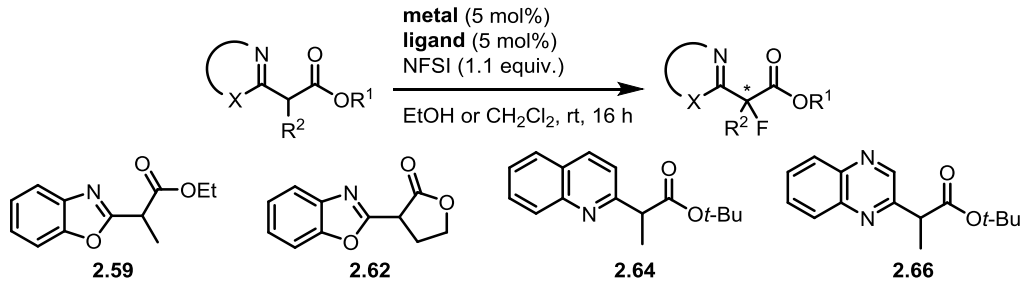
Ethanol had a comparatively high relative conversion whereas one could not be calculated for *iso*-propanol owing to complete suppression of the background reaction (*Table 2.04, entries 1 and 2*); however, *iso*-propanol also reduced the conversion of the catalysed reaction. Acetonitrile was a poor solvent choice for fluorination as the relative conversion

was small (*entry 3*). However, the relative conversions for diethyl ether and THF were comparable to ethanol (*entries 4 and 5*).

During screening it became apparent that NFSI had differing solubility in the various solvents screened. For example, NFSI was only partially soluble in ethanol and *iso*-propanol whereas it was completely soluble in acetonitrile. This might explain the high conversion observed for the uncatalysed reaction in acetonitrile (*entry 3*). With this in mind, ethanol was used in the following screening reactions.

2.2.5 Catalyst Screening

Substrates **2.59**, **2.62**, **2.64** and **2.66** were chosen as model substrates for screening as they contain a variety of heterocycles, which would potentially enable us to develop a *general* and highly enantioselective catalytic system (*Scheme 2.25*). All fluorinations were performed in ethanol or dichloromethane at room temperature (lactone **2.62** underwent ring-opening if the fluorination was performed in ethanol, and dichloromethane has previously been used to effect the highly enantioselective fluorination of lactones).[97]



Scheme 2.25. Catalyst screening for selected substrates

A variety of transition metal salts were screened, including those containing nickel, copper, silver, cobalt, iron and manganese, in combination with *N,N*-, *P,P*- and *N,P*-ligands (*Figure 2.08*). The majority of successful catalysts for enantioselective electrophilic fluorination rely on C_2-symmetric ligands, such as DPDM-BOX, Ph-PyBOX and BINAP, and thus these ligands provided a good starting point. However non-C_2-symmetric ligands were also explored, including (*S*)-*t*-BuPyOx and (*S*)-*i*-Pr-PHOX.

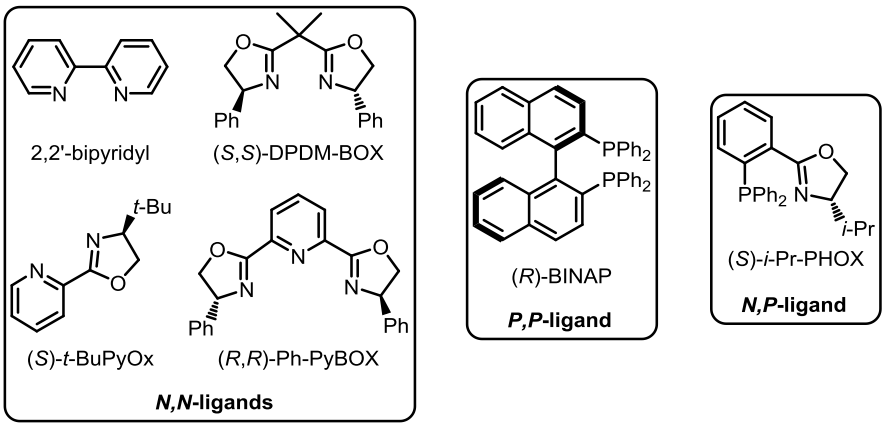
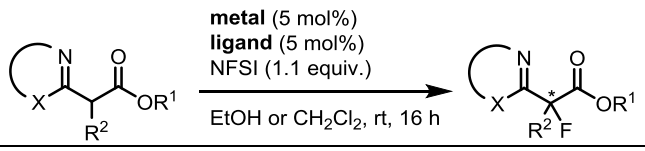
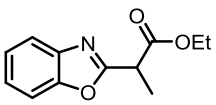


Figure 2.08. Ligand classes screened

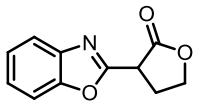
The majority of catalysts screened gave racemic products in low conversion, but amongst the metals screened there were high expectations for azaphilic nickel and copper, in the hope that these metals would successfully coordinate to the heterocyclic nitrogen to allow the creation of a well-defined chiral environment.

A variety of Ni(II) salts were screened with different ligand classes against benzoxazoles **2.59** and **2.62** (*Table 2.05*). The use of $Ni(ClO_4)_2$ in enantioselective electrophilic fluorinations is well documented,[101-102] and an excellent conversion of 99% for ethyl ester **2.59** with racemic ligand bipy was promising but switching to enantioenriched ligands (*S*)-*t*-BuPyOx and (*R*)-BINAP failed to induce any enantioselectivity (*Table 2.05*, *entries 1-3*). The results obtained with $Ni(OAc)_2 \cdot 4H_2O$ are perhaps the most insightful as this salt was screened against the widest variety of ligands. In the literature, $Ni(OAc)_2 \cdot 4H_2O$ has occasionally been used in place of $Ni(ClO_4)_2$;[102] perchlorate anions are more weakly coordinating than acetate anions (anion dissociation must occur prior to substrate association), and this is presumably the reason for the preferential use of $Ni(ClO_4)_2$. Pleasingly, with (*S*,*S*)-DPDM-BOX as ligand, a 75% conversion and 26% *ee*—the highest enantiomeric excess obtained during screening with Ni(II)—was observed using substrate **2.59** (*entry 4*). Unfortunately, switching from bidentate (*S*,*S*)-DPDM-BOX to tridentate (*R*,*R*)-Ph-PyBOX resulted in the loss of enantioselectivity (*entry 5*).





2.59



2.62

Entry	Metal	Ligand	Conv. (%)[a]	*ee*	Conv. (%)[a]	*ee*
1		bipy	99%	N/A[b]	-	-
2	$Ni(ClO_4)$	(*S*)-*t*-BuPyOx	-	-	80%	4%
3		(*R*)-BINAP	70%	0%	-	-
4		(*S*,*S*)-DPDM-BOX	75%	26%	-	-
5	$Ni(OAc)_2 \cdot 4H_2O$	(*R*,*R*)-Ph-PyBOX	67%	0%	-	-
6		(*R*)-BINAP	95%	0%	-	-
7		(*S*)-*i*-Pr-PHOX	78%	6%	-	-
8	$Ni(acac)_2$	bipy	79%	N/A[b]	-	-
9		(*R*)-BINAP	62%	0%	-	-
10	$Ni(OTf)_2$	(*R*)-BINAP	49%	0%	-	-

[a] conversion determined by GLC or ^{1}H NMR spectroscopy based on remaining substrate
[b] achiral ligand gave racemic product

Table 2.05. Selected screening results of Ni(II) salts

Owing to the different denticity of (*S*,*S*)-DPDM-BOX and (*R*,*R*)-Ph-PyBOX, these fluorinations will proceed through different transition-state structures. With Ni(II)-(*S*,*S*)-DPDM-BOX, it has been proposed that the fluorination of *β*-ketoester **2.90** proceeds through square pyramidal transition-state structure **TS-2.91**,[101] whereas with Ni(II)-(*R*,*R*)-Ph-DBFOX (another tridentate ligand), fluorination proceeds through octahedral transition-state structure **TS-2.92** (*Figure 2.09*).[102] For substrate **2.59**, **TS-2.92** may not provide adequate distinction between its enantiotopic faces.

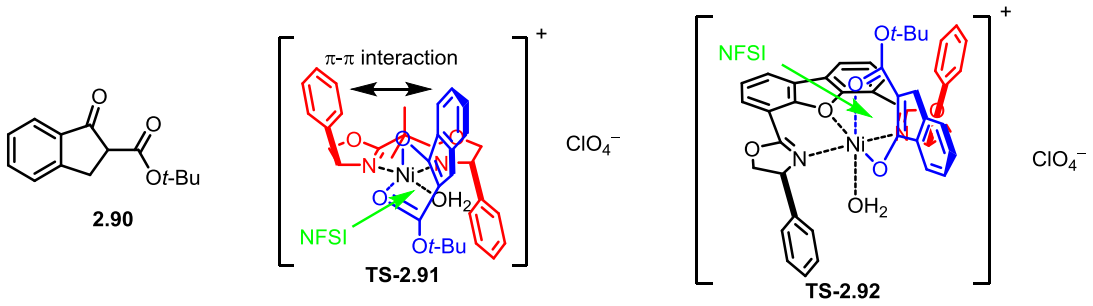
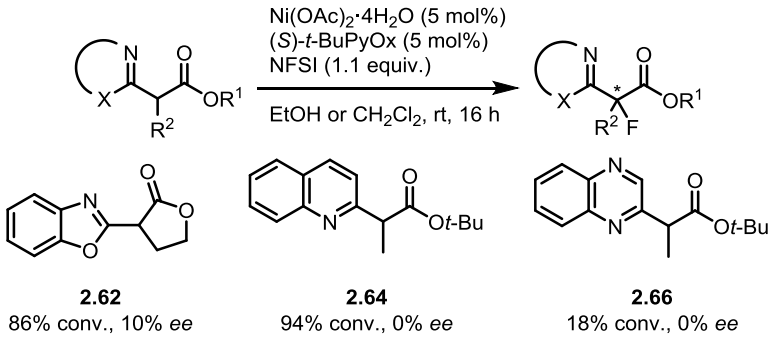


Figure 2.09. Different transition-state structures for **2.90** with BOX and DBFOX ligands

(*S*)-*t*-BuPyOx, a non-C_2-symmetric ligand, also fared poorly with $Ni(OAc)_2 \cdot 4H_2O$; of the

three substrates tested, only one (**2.62**) gave rise to non-racemic product and even then in only 10% *ee* (*Scheme 2.26*).

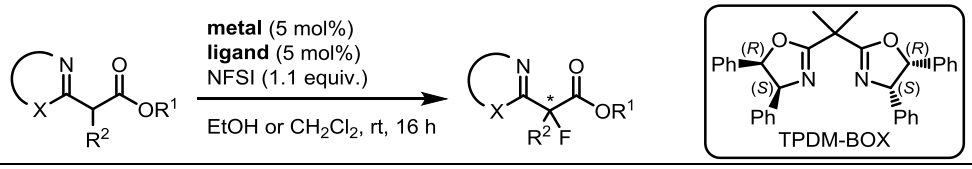


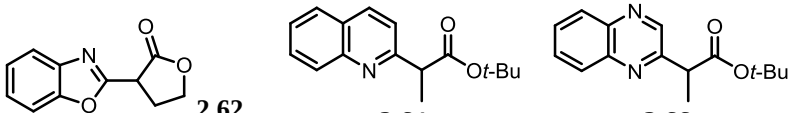
Scheme 2.26. Screening with (*S*)-*t*-BuPyOx

Screening with (*R*)-BINAP again gave rise to racemic product and matters did not improve greatly with *N*,*P*-ligand (*S*)-*i*-Pr-PHOX, as stereoinduction was poor giving the product in only 6% *ee* (*Table 2.05, entries 6 and 7*).

$Ni(acac)_2$ and $Ni(OTf)_2$ gave similarly disappointing results with (*R*)-BINAP, and only served to highlight the incompatibility of Ni(II) with *P*,*P*-ligands (*entries 8-10*).

At this point attention turned to copper in the hope that this similarly azaphilic metal would fare better than nickel (*Table 2.06*).





2.62 **2.64** **2.66**

Entry	Metal	Ligand	Conv. (%)[a]	*ee*	Conv. (%)[a]	*ee*	Conv. (%)[a]	*ee*
1	$Cu(OTf)_2$	(*R*)-BINAP	-	-	-	-	nd[b]	-
2		(*S*,*S*)-DPDM-BOX	-	-	-	-	nd[b]	-
3		TPDM-BOX	82%	28%	100%	0%	49%	0%
4		(*S*)-*t*-BuPyOx	82%	26%	100%	0%	54%	0%
5	$Cu(OAc)_2$	(*S*)-*t*-BuPyOx	76%	10%	100%	8%	67%	0%

[a] conversion determined by GLC or ^1H NMR spectrometry based on remaining substrate
[b] complex mixture of products

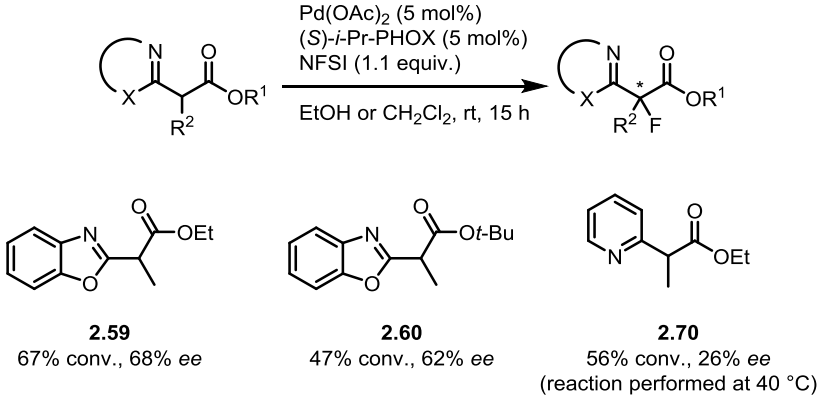
Table 2.06. Selected screening results of Cu(II) salts

In addition to the ligands given in *Figure 2.08*, TPDM-BOX was also screened. TPDM-BOX

contains two more phenyl groups than (*S*,*S*)-DPDM-BOX and it was hoped that this additional steric bulk would improve the level of stereoinduction.

Again, $Cu(OTf)_2$ was chosen owing to its success in previous enantioselective electrophilic fluorinations.[101] Unfortunately, no meaningful results could be obtained with (*R*)-BINAP and (*S*,*S*)-DPDM-BOX as the crude ^{1}H NMR spectrum revealed a complex mixture of products for substrates **2.59**, **2.60** (not shown in *Table 2.06*) and **2.66** *(Table 2.06, entries 1 and 2*). Switching to TPDM-BOX pleasingly gave rise to non-racemic products; 82% of lactone **2.62** underwent fluorination to generate product in 28% *ee* (*entry 3*). It was also gratifying to observe that the non-C_2-symmetric ligand (*S*)-*t*-BuPyOx performed equally as well as the C_2-symmetric TPDM-BOX (*entry 4*). Switching the Cu(II) source to $Cu(OAc)_2$ gave mixed results; whilst the *ee* of fluorinated lactone **2.62** decreased from 26% to 10%, some *ee* was now obtained for fluorinated quinoline **2.64** (*entry 5*).

Palladium is generally more compatible with phosphorus containing ligands than either nickel or copper, and as *i*-Pr-PHOX is a *N*,*P*-ligand, this ligand was screened with $Pd(OAc)_2$ (*Scheme 2.27*). Esters **2.59** and **2.60** were fluorinated in 67% conversion with 68% *ee*, and in 47% conversion with 62% *ee* respectively. Enantioselectivity was also conferred in the fluorination of pyridine **2.70**, but the reaction had to be performed at 40 °C in order to observe an appreciable conversion of 56%.



Scheme 2.27. Screening with (*S*)-*i*-Pr-PHOX ligand

Whilst a general catalyst remained elusive, spurred on by the success of the palladium-catalysed system, all substrates were fluorinated with palladium-BINAP catalyst

2.08a developed in 2002 by Sodeoka and co-workers (*Figure 2.10*).[97] This catalyst is relied upon for the preparation of fluorine stereocentres in excellent yield and selectivity[97] and is commercially available and relatively inexpensive.[131]

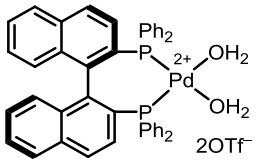
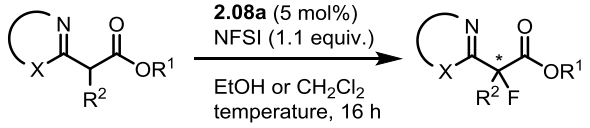


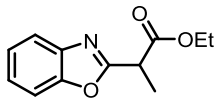
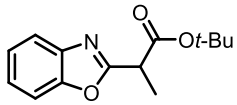
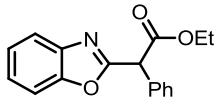
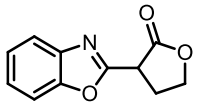
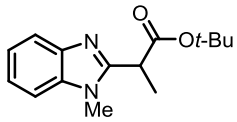
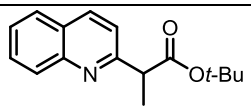
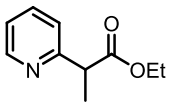
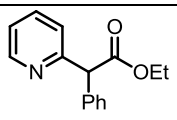
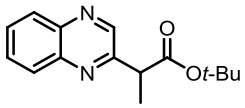
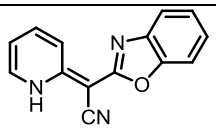
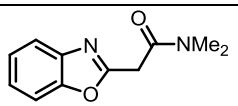
Figure 2.10. Catalyst **2.08a** developed by the Sodeoka group

2.2.5.1 Screening with [((*R*)-BINAP)Pd(OH_2)$_2$]$^{2+}$2OTf$^-$

We began by screening all substrates that had been prepared to date (see *section 2.2.3*) with catalyst **2.08a** (*Table 2.07*). As well as enabling a comparison between azaarylacetates and amides with the substrates reported in the literature, performing such a thorough screen would allow the reactivity of individual substrates to be accurately compared. Once again, the fluorinations were conducted in ethanol with the exception of lactone **2.62**, which was performed in dichloromethane.

Benzoxazole ethyl ester **2.59** was fluorinated at 0 °C (maintained using a cryostat) with complete conversion of starting material and in 90% *ee* (*Table 2.07*, *entry 1*); a similarly excellent conversion and enantioselectivity (82% *ee*) was observed for benzoxazole *tert*-butyl ester **2.60** (*entry 3*). Lowering the reaction temperature to –20 °C pleasingly resulted in an increase in *ee* (92% for the fluorination of ethyl ester **2.59** and 90% for *tert*-butyl ester **2.60**) (*entries 2 and 4*). When methyl was switched for a phenyl substituent (**2.61**), a 100% conversion of substrate was again apparent, but to the detriment of the enantioselectivity (8% *ee*) (*entry 5*). Presumably, the phenyl substituent enhances the acidity of the α-phenyl proton to such an extent that the uncatalysed background reaction proceeds at a much faster rate than the catalytic fluorination, reducing the enantiomeric excess of the product. In an effort to minimise the background reaction, the reaction was repeated at −20 °C and this allowed the preparation of the product in 80% yield and 76% *ee* (*entry 6*).



Entry	Substrate	Solvent	Temperature	Conv. (%)[a]	Yield (%)	*ee*
1	 **2.59**	EtOH	0 °C	100%	nd	90%
2			–20 °C	100%	42%	92%
3	 **2.60**	EtOH	0 °C	100%	nd	82%
4			–20 °C	96%	72%	90%
5	 **2.61**	EtOH	rt	100%	nd	8%
6			–20 °C	100%	80%	75%
7	 **2.62**	CH_2Cl_2	rt	100%	63%	93%
8			–20 °C	94%	nd	96%
9	 **2.63**	CH_2Cl_2	50 °C	19%	nd	10%
10	 **2.64**	EtOH	rt	89%	nd	0%
11			–20 °C	47%	nd	0%
12	 **2.70**	EtOH	rt	22%	nd	14%
13	 **2.72**	EtOH	rt	88%	nd	0%
14			–20°C	43%	nd	6%
15	 **2.66**	EtOH	rt	45%	nd	0%
16	 **2.88**	EtOH	rt	100%	nd	4%
17			–20°C	90%	nd	12%
18	 **2.93**	EtOH	–20°C	56%	nd	86%

[a] conversion determined by ^{1}H NMR spectroscopy based on remaining substrate

Table 2.07. Selected screening results with [((*R*)-BINAP)Pd$(OH_2)_2]^{2+}2OTf^-$ **2.08a**

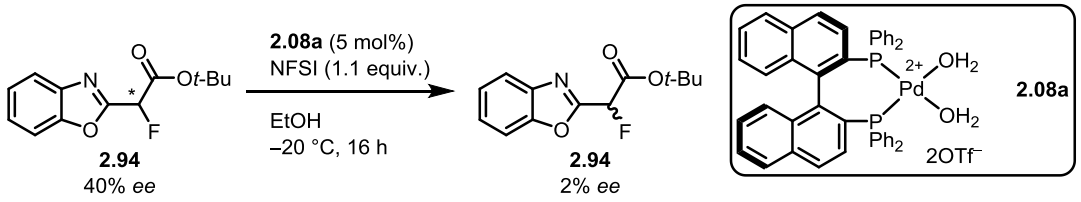
Lactone **2.62** underwent smooth conversion into product (100%) and the product was obtained in 63% yield and a remarkable 93% *ee* at room temperature (*entry 7*); lowering the temperature resulted in an increase in *ee* to 96% (*entry 8*). This excellent result is presumably because the transition state for a substrate with a five-membered lactone is more rigid than one for an acyclic ester substrate.

Attention then turned to the remaining azaarylacetates, but disappointingly low conversion and stereoinduction was apparent for all these substrates. Benzimidazole **2.63** proved unreactive at room temperature and it was only after raising the reaction temperature to 50 °C that a poor 19% conversion and 10% *ee* was observed (*entry 9*). Although 89% of quinoline **2.64** underwent fluorination at room temperature, the product was racemic (*entry 10*). The background reaction could be significant in this case, and the fluorination was repeated at –20 °C (*entry 11*), but this only resulted in a reduction in conversion (47%) with no stereoinduction.

The fluorination of pyridine **2.70** served to highlight the reactivity difference between itself and the benzannulated derivative **2.64** (*entry 12*): pyridine **2.70** proved to be much less reactive than quinoline **2.64**, with only 22% of substrate undergoing fluorination in 14% *ee*. Given this result, it was hoped phenyl derivative **2.72** would be more reactive due to the enhanced acidity of the α-phenyl proton. Although an improved conversion was observed, pyridine **2.72** was fluorinated with poor enantioselectivity, at both room temperature and –20 °C (*entries 13 and 14*). Quinoxaline **2.66** was also poorly reactive and only 45% of substrate underwent fluorination to generate racemic product (*entry 15*).

Pyridyl benzoxazole **2.88** was then tested (*entries 16 and 17*). At room temperature, all starting material was consumed (discernible by the disappearance of the NH signal at 15.52 ppm in the crude ^{1}H NMR spectrum) but the product was formed in 4% *ee*. Lowering the reaction temperature to –20 °C resulted in a slight drop in conversion (90%) and increase in *ee* to 12%. The low enantioinduction is presumably as a result of the high background reaction for a substrate which is predominately the enamine tautomer.

Finally, amide **2.93** (which was readily available within the group) was subjected to fluorination and although only 56% of the starting material underwent conversion, the product was generated in 86% *ee* (*entry 18*). However, we were mindful that the product might be subject to racemisation under the reaction conditions, as the *ee* of fluorinated ester **2.94** (also lacking an *α*-fluoro substituent) decreased from 40% to 2% when resubmitted to $[((R)\text{-BINAP})Pd(OH_2)_2]^{2+}2OTf^-$ over 16 hours (*Scheme 2.28*).



Scheme 2.28. Racemisation of fluorinated amide under the reaction conditions

Other examples of poorly reactive substrates which are not given in the table include pyrazines **2.67** and **2.68**, isoquinoline **2.65**, benzisoxazole **2.75**, quinoxalinone **2.78** and thiadiazoles **2.82** and **2.83** (*Figure 2.11*). Certainly for isoquinoline **2.65** and benzisoxazole **2.75**, steric clashing between the methyl group and the aryl hydrogens in the planar intermediate may be of significance and discourage the formation of the enamine intermediate. Enamine **2.95** depicts the perceived and unfavourable steric interactions for the isoquinoline **2.65** intermediate.

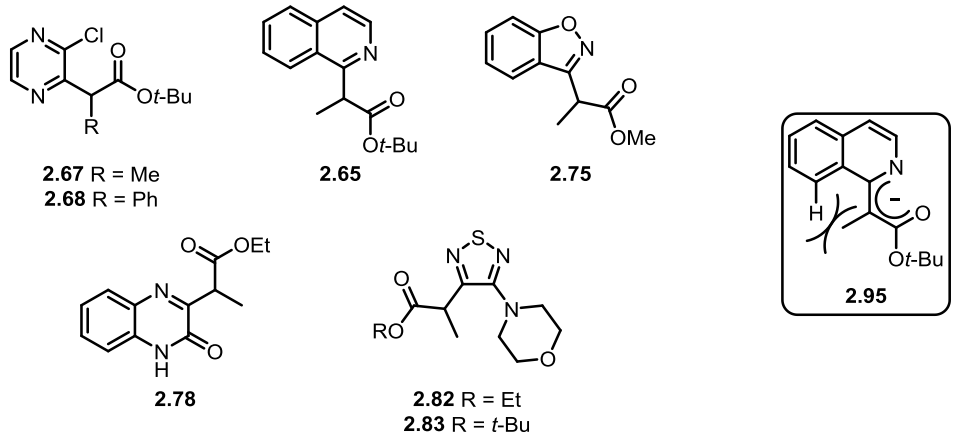


Figure 2.11. Unreactive substrates

From screening with the commercial palladium catalyst, one clear observation regarding substrate scope can be drawn: only benzoxazoles are capable of being fluorinated with high

enantioselectivity, raising the possibility that these substrates are coordinating to palladium through oxygen and not through nitrogen.

In 1983, Massacesi and co-workers came to a similar conclusion when investigating the binding of benzoxazole and 2-methylbenzoxazole in Pd(II) and Pt(II) complexes.[132] From IR analysis, they found that in ML_2X_2 complexes (where M = Pd(II), Pt(II); L = benzoxazole, 2-methylbenzoxazole; X = Cl, Br, I, NO_3, SCN), both L ligands were monodentate *but* benzoxazole behaved as *N*-bound whereas 2-methylbenzoxazole behaved as *O*-bound. Their findings gained further support during the investigation of Pd(mal)L complexes (mal = malonate, L = benzoxazole, 2-methylbenzoxazole) where IR analysis once again showed benzoxazole to be binding through nitrogen, and 2-methylbenzoxazole through oxygen.[133]

With this mind, a tentative transition state for the fluorination of benzoxazole lactone **2.62** is proposed (*Figure 2.12*), based on the one suggested by Sodeoka and co-workers for fluorination of *β*-ketoesters.[97] If lactone **2.62** orientates itself so that the benzoxazole moiety minimises any steric interactions with the phosphine aryl groups and fluorination occurs on the *re* face, then this would lead to fluorinated lactone **2.96** as a single enantiomer (the absolute stereochemistry of the fluorinated stereocentre has not been determined).

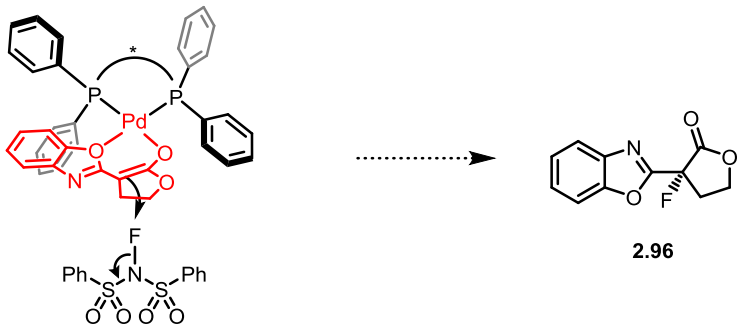


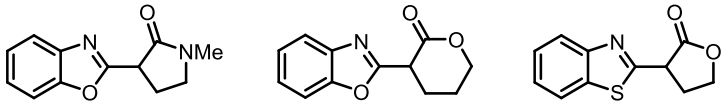
Figure 2.12. Proposed transition-state structure for lactone **2.62**

In an effort to further explore substrate-catalyst binding, a series of targeted oxygen-containing substrates were synthesised.

2.2.5.1.1 Synthesis of Targeted Substrates and their Fluorinations

Substrates **2.97**-**2.99** were targeted, which would probe the role of both the heterocycle and ester moiety (*Figure 2.13*). Lactam **2.97** would explore whether a lactam could be

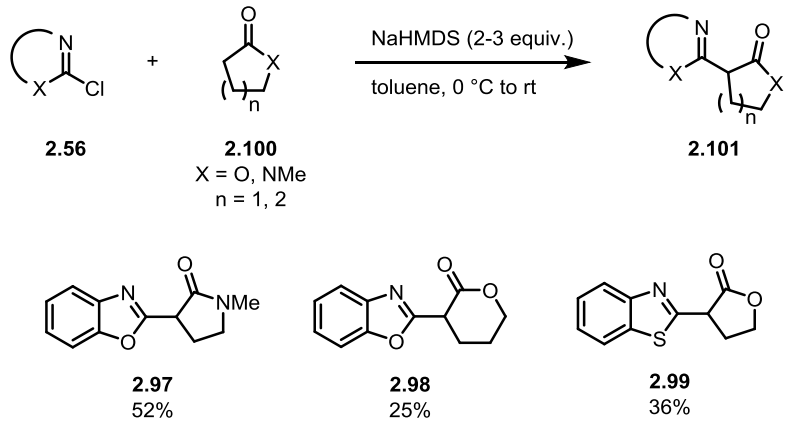
substituted for a lactone, and lactone **2.98** would investigate the effect of a six-membered lactone ring on the fluorination transition-state structure and the resultant stereochemical outcome of the reaction. To probe whether the heterocyclic oxygen was in fact responsible for the high enantioselectivity described for the benzoxazoles in *section 2.2.5.1*, benzothiazole **2.99** was targeted (where the oxygen in benzoxazole has been replaced with sulfur).



2.97 **2.98** **2.99**

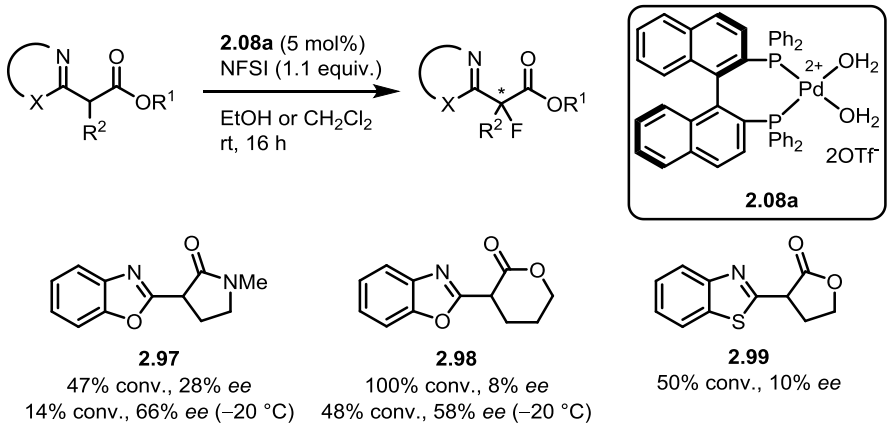
Figure 2.13. Targeted substrates

These substrates were synthesised using the same method as that described for the synthesis of substrates **2.59**-**2.68** (see *section 2.2.3*), namely the addition of esters and amides **2.100** to heterocylic chlorides **2.56** (*Scheme 2.29*). Using this general method, lactam **2.97** was successfully prepared from 2-chlorobenzoxazole **2.85** and the common laboratory solvent *N*-methylpyrrolidine in 52% yield. However, the yields obtained for the lactones **2.98** and **2.99** were not as gratifying. Although the successful synthesis of lactone **2.98** was apparent from the crude ^{1}H NMR spectrum, purification by column chromatography failed to separate it from an unknown impurity and recrystallisation of this material was required to give **2.98** as a pure white powder in 25% yield. Benzothiazole lactone **2.99** was only prepared in 36% yield; from previous attempted syntheses, we suspect benzothiazole esters are an unstable class of compounds and the low yield is probably a reflection of this. With this foreknowledge, **2.99** was fluorinated immediately following its preparation.



Scheme 2.29. Synthesis of targeted oxygen-containing substrates

The targeted substrates were then fluorinated with $[((R)\text{-BINAP})Pd(OH_2)_2]^{2+}2OTf^-$ (*Scheme 2.30*). As expected, lactam **2.97** was fluorinated enantioselectively but with only 47% conversion and 28% *ee* at room temperature. This is in stark contrast to the fluorinated five-membered lactone **2.62**—product **2.96** was isolated in 63% yield and 93% *ee*. All things considered, an enantiomeric excess of 28% is still in support of the argument that benzoxazoles bind to the catalyst through oxygen, given that the nitrogen-containing substrates were only fluorinated in up to 14% *ee* with the same catalyst. However, the reduction in *ee* could be a consequence of the *N*-methyl group in the transition state—additional steric interactions could distort the proposed transition state for lactone **2.62** so that the two enantiotopic faces of the enamide are less distinguishable. Pleasingly, lowering the reaction temperature resulted in an increase in *ee* to 66% but with only an accompanying 14% conversion.



Scheme 2.30. Fluorination of targeted substrates

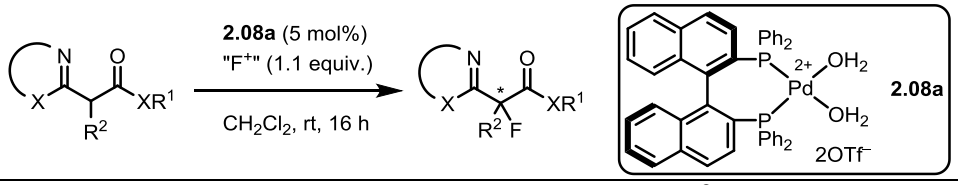
The fluorination of six-membered lactone **2.98** was initially somewhat disappointing as the product was only prepared in 8% *ee*. However the ^{1}H NMR spectrum of lactone **2.98** in $CDCl_3$ had previously revealed it to be a mixture of keto-enol form and so it would not be surprising if the background reaction for this substrate occurred at a competitive rate. Pleasingly, lowering the reaction temperature to –20 °C resulted in an increase in *ee* to 58%, again providing support for the benzoxazole binding argument. For this substrate there is an even greater reactivity difference between the five- and six-membered lactones (**2.62** and **2.98**) than between lactone **2.62** and lactam **2.97**. Whereas the five-membered lactone **2.62** is fluorinated in 93% *ee* at room temperature, only at –20 °C is an appreciable level of enantioselectivity (58% *ee*) achieved for the six-membered analogue **2.98**. The lower *ee* can be explained in two ways: either the background reaction is still occurring at –20 °C, or the transition state is less rigid than the one proposed for the five-membered lactone **2.62**, owing to the presence of a longer and more flexible lactone tether.

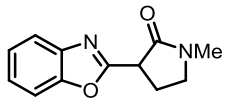
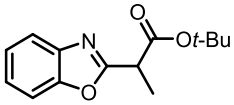
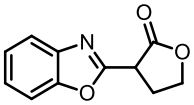
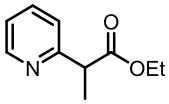
Finally, benzothiazole lactone **2.99** was subjected to fluorination and gave product in poor *ee* (10%). Whilst this could be attributed to the absence of oxygen in the heterocycle, sulfur could also be poisoning the palladium catalyst.[134]

2.2.5.1.2 Screening with Alternative Fluorinating Agents

Alternative fluorinating agents Selectfluor® and *N*-fluoropyridinium salt were also screened with $[((R)\text{-BINAP})Pd(OH_2)_2]^{2+}2OTf^-$ (*Table 2.08*). The *N*-fluoropyridinium salt was generated *in situ* from Selectfluor® and pyridine, and all reactions were conducted in CH_2Cl_2 at room temperature. Remarkably in all reactions using Selectfluor®, the enantiomer obtained was of the opposite configuration to that obtained using NFSI. In some cases, the magnitude of the *ee* was substantially different. For example, the fluorinated product for lactam **2.97** was isolated in 28% *ee* of one configuration using NFSI and 60% *ee* of the opposite configuration using Selectfluor® (*Table 2.08, entry 1*). Similarly, there was a marked difference for ester **2.60** (66% and 93% *ee* of the two enantiomers, *entry 2*). Low conversion

for ester **2.60** was observed using pyridine and Selectfluor® and so this fluorinating agent was not investigated any further. Consistent magnitudes of enantioselectivity were recorded with some substrates; lactone **2.62** gave both enantiomers in excellent *ee* whilst pyridine **2.70** gave both enantiomers in low *ee*, using NFSI and Selectfluor® (*entries 3 and 4*).



		NFSI		Selectfluor®		Pyridine/Selectfluor®	
Entry	**Substrate**	**Conv. (%)[a]**	***ee***	**Conv. (%)[a]**	***ee*[b]**	**Conv. (%)[a]**	***ee***
1	 **2.97**	47	28%	49	60%	-	-
2	 **2.60**	60	66%	77	93%	6	nd
3	 **2.62**	100	93%	90	85%	-	-
4	 **2.70**	22[c]	14%	24	38%	-	-

[a] conversion determined by ^{1}H NMR spectroscopy based on remaining substrate
[b] opposite enantiomer obtained with Selectfluor®
[c] reaction conducted in EtOH

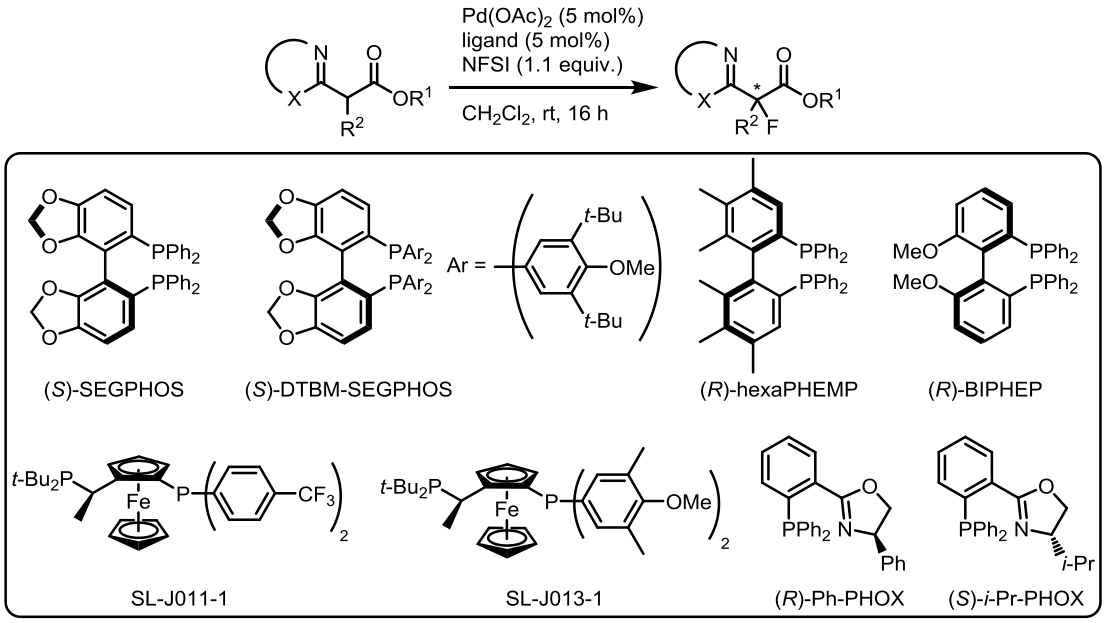
Table 2.08. Alternative fluorination sources

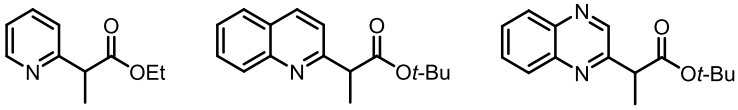
These differences in product configuration could be explained if different steric interactions are operating between the substrate-catalyst and fluorinating agent in the transition-state structure (see *Figure 2.12*). Smaller fluorinating agents may be able to approach the substrate from one face whilst bigger fluorinating agents may be forced to approach the substrate from the opposite face, owing to more significant steric interactions in the transition-state structure.

2.2.5.2 Screening Palladium with Other Ligands

Owing to the success of the palladium-catalysed fluorination of benzoxazole-containing

substrates, other ligands for palladium were explored in the hope of developing a more general protocol for azaarylacetates and amides (*Table 2.09*).





2.70 **2.64** **2.66**

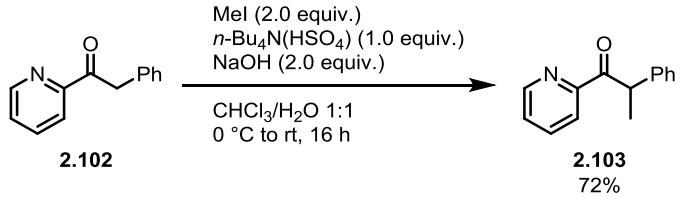
Entry	Ligand	*ee*	*ee*	*ee*
1	(*S*)-SEGPHOS	14%	-	-
2	(*S*)-DTBM-SEGPHOS	7%	-	4%
3	(*R*)-hexaPHEMP	12%	0%	0%
4	(*R*)-BIPHEP	10%	0%	0%
5	SL-J011-1	0%	0%	0%
6	SL-J013-1	0%	0%	0%
7	(*R*)-Ph-PHOX	12%	0%	0%
8	(*S*)-*i*-Pr-PHOX	8%	0%	0%

Table 2.09. Screening palladium with other ligands

Only challenging substrates were screened that did not contain heterocyclic oxygen and only *ee* values for products were obtained to increase screening efficiency. Palladium acetate was used as the Pd(II) source throughout. Low enantioselectivities were observed for all ligands screened and quinoline **2.64** and quinoxaline **2.66** generally gave racemic products. Pyridine **2.70** was the only substrate to consistently yield non-racemic products, although the maximum *ee* was only 14%, obtained using (*S*)-SEGPHOS (*Table 2.09, entry 1*).

2.2.6 α-Ketoazaarenes

Finally, α-ketoazaarene **2.103** was investigated as an alternative substrate to β-ketoazaarenes. Sodeoka and co-workers had previously demonstrated the successful enantioselective fluorination of α-ketoesters and it was hoped that the five-membered chelate in the transition catalyst would lead to a product in high *ee*.[120] Ketone **2.103** was synthesised in 72% yield from precursor **2.102** in a methylation reaction (*Scheme 2.31*).[135]



2.102 **2.103** 72%

Scheme 2.31. Synthesis of α-ketoazaarene **2.106**

Ketone **2.103** was subjected to fluorination under two sets of conditions (*Table 2.10*); the first using $[((R)\text{-BINAP})Pd(OH_2)_2]^{2+}2OTf^-$ that had been successfully applied to benzoxazole β-ketoazaarenes and the second using $Ni(OAc)_2$ and TPDM-BOX, a catalyst that had been applied in the highly enantioselective Michael addition reactions of similar substrates with nitroalkenes.[136] Both sets of conditions were low yielding but the enantioselectivities were appreciable, with $Ni(OAc)_2 \cdot 4H_2O$-TPDM-BOX giving an *ee* of 45%. Although these results were promising, α-ketoazaarenes were not pursued any further, but they remain a possible future area of investigation.

2.103 **2.104**

Entry	Catalyst	% Conv.[a]	*ee*
1	$[((R)\text{-BINAP})Pd(OH_2)_2]^{2+}2OTf^-$	25	37%
2	$Ni(OAc)_2 \cdot 4H_2O$-TPDM-BOX	10	45%

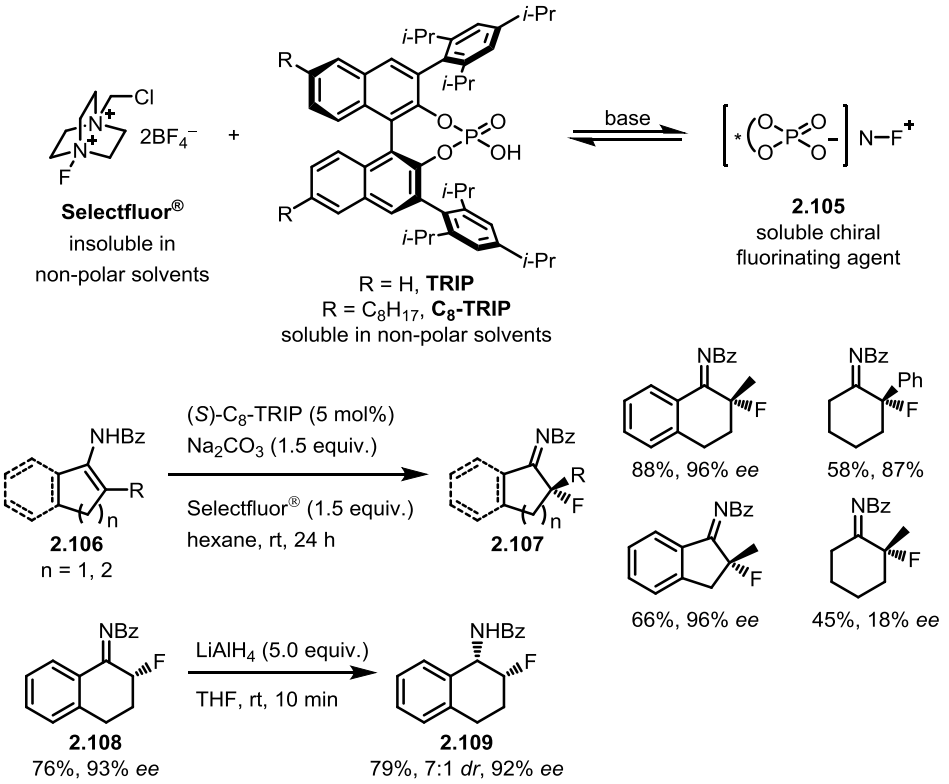
[a] conversion determined by ^1H NMR spectroscopy based on remaining substrate

Table 2.10. Fluorination of α-ketoazaarene **2.103**

2.2.7 Fluorination of Enamides

After the completion of this project, Toste and co-workers reported the use of an enamide functionality for the activation and enantioselective fluorination of benzoyl-protected enamides **2.106** to α-fluoroimines **2.107** using anionic phase transfer catalysis

(*Scheme 2.32*).[137]

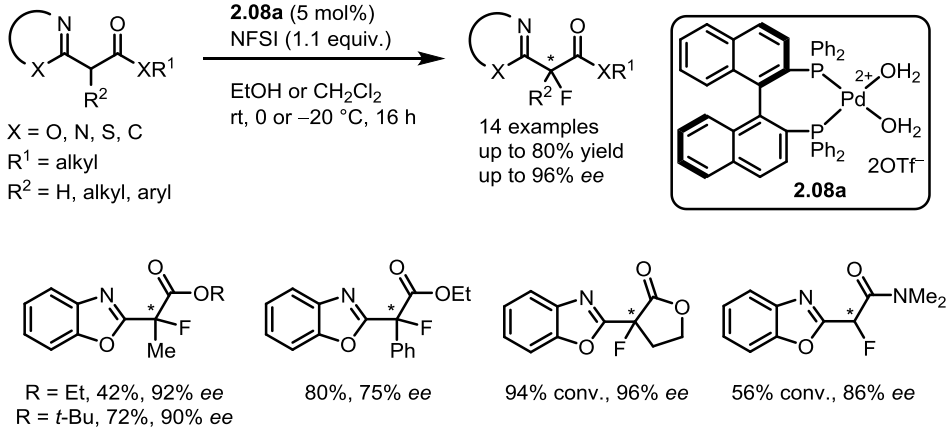


Scheme 2.32. Anionic phase transfer catalysis for the enantioselective fluorination of enamides **2.106**

In this strategy the fluorinating agent Selectfluor®, which is insoluble in non-polar solvents, is solvated by phase transfer catalyst TRIP to generate chiral fluorinating agent **2.105** *in situ*, which is soluble in non-polar solvents. The choice of nitrogen protecting group was critical, as in addition to giving the product in high *ee*, it was essential that the resultant imine functionality remain intact to allow subsequent manipulation. A range of fluorinated products were consistently generated in excellent *ee* but for 2-alkyl cyclohexanone derivatives, enantioselectivity was poor. To demonstrate the utility of this methodology, product **2.108** was subsequently reduced to amine **2.109**.

2.3 Conclusions

Through screening with $[((R)\text{-BINAP})Pd(OH_2)_2]^{2+}2OTf^-$, 2-fluorobenzoxazolyl acetates have been prepared in up to 96% *ee*, although this high level of stereoselectivity did not extend to non-benzoxazole containing azaarenes (*Scheme 2.33*).



Scheme 2.33. Enantioselective fluorination of azaarylacetates and amides

From these results, the substrate is proposed to bind to the catalyst through the oxygen of the benzoxazole and not through the nitrogen as might be expected (*Figure 2.13*). A series of targeted substrates were prepared and fluorinated, which provided further support for the argument. However, other factors could be at play for those products prepared in poor enantioselectivity.

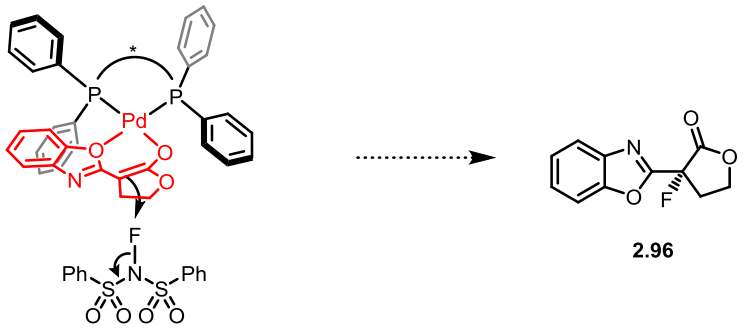
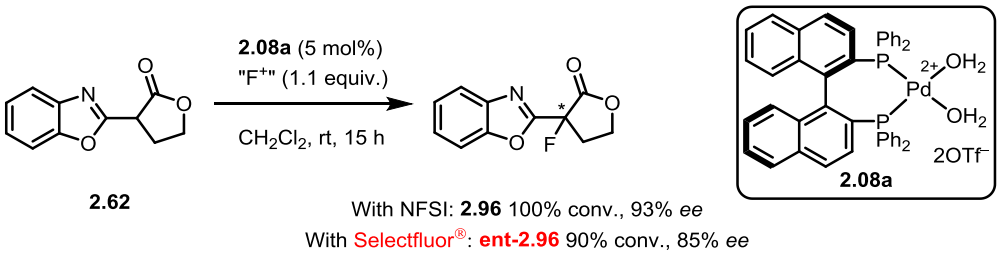


Figure 2.13. Benzoxazole binding to catalyst through heterocyclic oxygen

Screening with alternative fluorinating agents revealed that opposite enantiomers could be accessed using NFSI and Selectfluor®, thus further demonstrating the potential of this methodology (*Scheme 2.34*).



Scheme 2.34. Enantioselectivity switch with NFSI and Selectfluor®

To conclude, a highly enantioselective fluorination method was developed for the

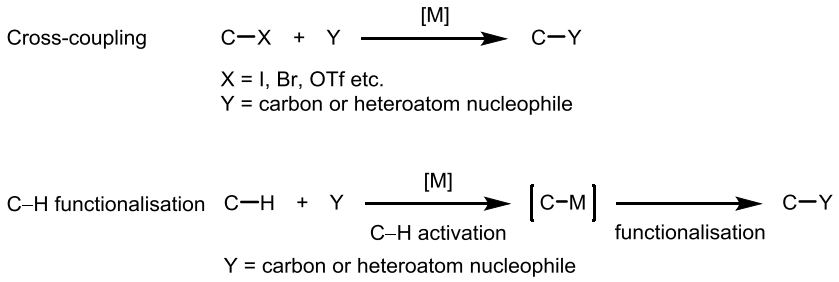
preparation of novel 2-fluorobenzoxazolyl acetates in which both enantiomeric products could be accessed. Attention then turned to another palladium-catalysed reaction, the oxidative annulation of ferrocene derivatives, for the preparation of novel highly functionalised products.

Chapter 3. Oxidative Annulation of Ferrocene Derivatives

3.1 Introduction

3.1.1 C–H Functionalisation

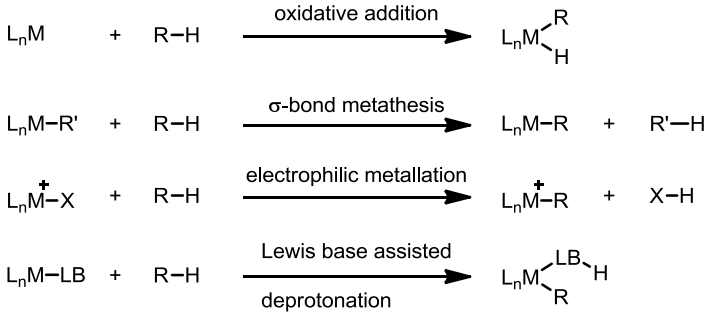
In recent years, C–H functionalisation has become an important strategy in organic synthesis and is rapidly becoming a realistic alternative to traditional cross-coupling reactions (*Scheme 3.01*).[138-149] Unlike cross-coupling, C–H functionalisation rarely requires substrate prefunctionalisation making it a potentially more efficient approach.[138] The majority of reported C–H functionalisations have been catalysed by late second- and third-row transition-metals, including palladium,[138, 140, 150-153] ruthenium[142, 147, 154] and rhodium;[155-158] however, there is a growing appreciation for the use of first-row transition-metal catalysts.[159] Palladium in particular has been highly successful in the fields of sp^2 and sp^3 C–H functionalisation, owing to the compatibility of Pd(II) with oxidants (often needed for the regeneration of Pd(II) in the catalytic cycle) and ambient air and moisture.



Scheme 3.01. Cross-coupling and C–H functionalisation

Depending on the metal used, in addition to the ligand, substrate, solvent, and additives, different mechanisms for the C–H activation step have been proposed (*Scheme 3.02*).[160-161] For electron-rich late transition-metals, oxidative addition is the most likely pathway as the changes in oxidation state and geometry of the metal in the product are energetically feasible. σ-Bond metathesis is favoured for early transition-metals in which a d^0 electronic configuration negates oxidative addition. Similarly, for electron-poor late transition-metals, electrophilic metallation (a formal equivalent of σ-bond metathesis) is more likely. Catalysts bearing Lewis basic ligands, such as a carboxylate, can facilitate C–H functionalisation *via*

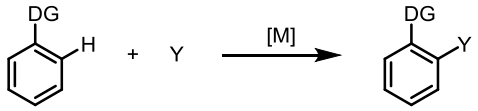
base assisted deprotonation.[142, 162-164]



Scheme 3.02. C–H activation mechanisms

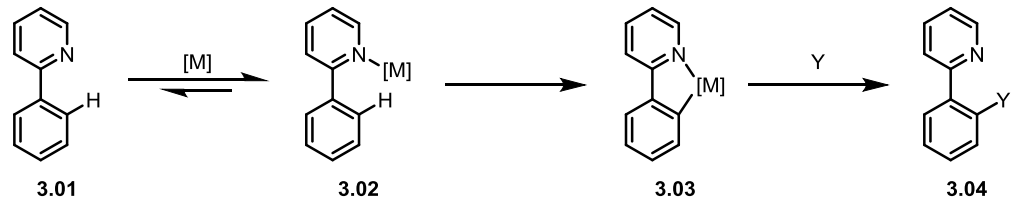
3.1.1.1 Directing Groups

Ideally, an unactivated C–H bond is transformed into a carbon–carbon or carbon–heteroatom bond.[145] However, a directing group is often required to coordinate the metal catalyst to effect C–H functionalisation. Coordination enhances the rate of reaction by increasing the proximity of the metal to the C–H bond and governs the regioselectivity of reaction—the majority of C–H functionalisation occur *ortho* to the directing group (*Scheme 3.03*). One disadvantage of using this strategy is that installation and manipulation of the directing group is often required.



Scheme 3.03. Directed C–H functionalisation

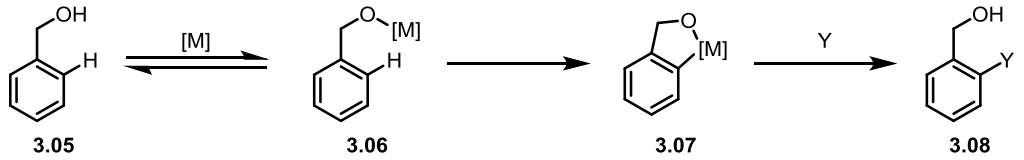
A variety of directing groups have been used, mainly nitrogen, sulfur and phosphorus based (for example, pyridine, oxazoline, sulfide and phosphine directing groups), which are strong σ-donors and/or π-acceptors. These are considered strong directing groups, as the corresponding metallacycles (e.g. **3.03**) are thermodynamically stable and less reactive towards subsequent functionalisation (*Scheme 3.04*).[165]



Scheme 3.04. Pyridine as a strong directing group

Directing groups based on oxygen heteroatoms (for example, alcohol, ketone and carboxylic

acid directing groups), are considered weak directing groups and have typically not been as well studied (*Scheme 3.05*).[165-167] The analogous metallacycles (e.g. **3.07**) are more challenging to form but less thermodynamically stable than **3.03**, making them more reactive towards functionalisation.



3.05 **3.06** **3.07** **3.08**

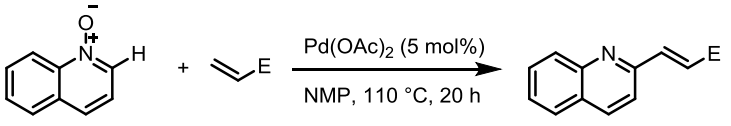
Scheme 3.05. Alcohol as a weak directing group

Owing to the often oxidative nature of C–H functionalisation, the catalyst often has to be regenerated in the catalytic cycle (e.g. Pd(0) to Pd(II)), and this is most commonly achieved using a stoichiometric amount of an external oxidant such as Cu(II) salts,[168-169] Ag(I) salts,[170-171] bis(acetoxy)iodobenzene,[172-173] benzoquinone,[174-175] persulfate salts[176-177] and oxygen.[178-179] This is not only atom inefficient but can limit the substrate scope of the reaction, owing to the incompatibility of certain functional groups with strong oxidants.[143]

An alternative to a stoichiometric external oxidant is a directing group which can itself act as an oxidant (an internal oxidant). In addition to waste minimisation, reactivity and selectivity can also be improved.[180]

3.1.1.1.1 Oxidising Directing Groups

The redox-neutral strategy of oxidising directing groups was independently realised by the groups of Cui and Wu,[181] Hartwig,[182] Yu,[183] and Guimond and Fagnou.[184] For example, Cui and Wu demonstrated that *N*-oxide can both act as a directing group and an oxidant in the alkenylation of quinoline *N*-oxide **3.09** (*Scheme 3.06*).

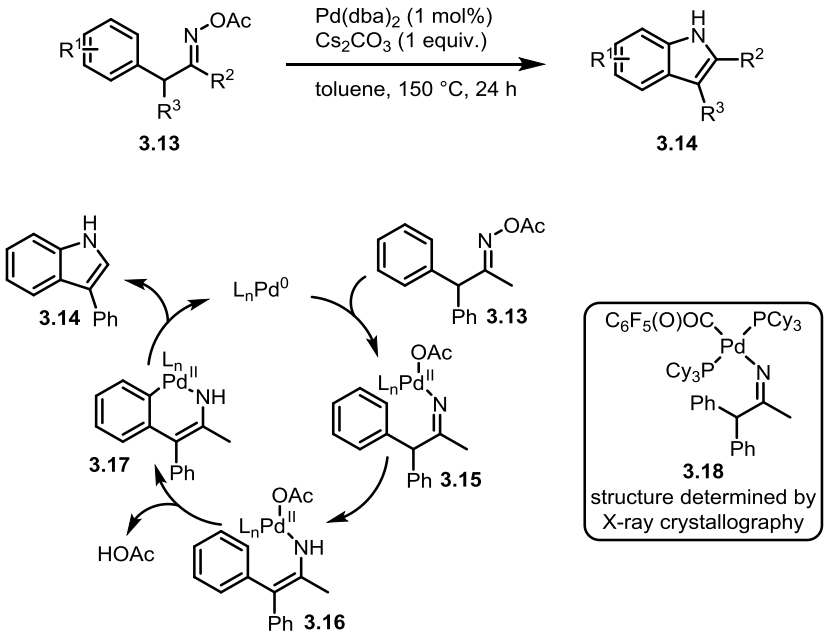


3.09 **3.10** **3.11**, E = CO_2Et, 86%
3.12, E = CN, 65%

Scheme 3.06. *N*-Oxide as an oxidising directing group

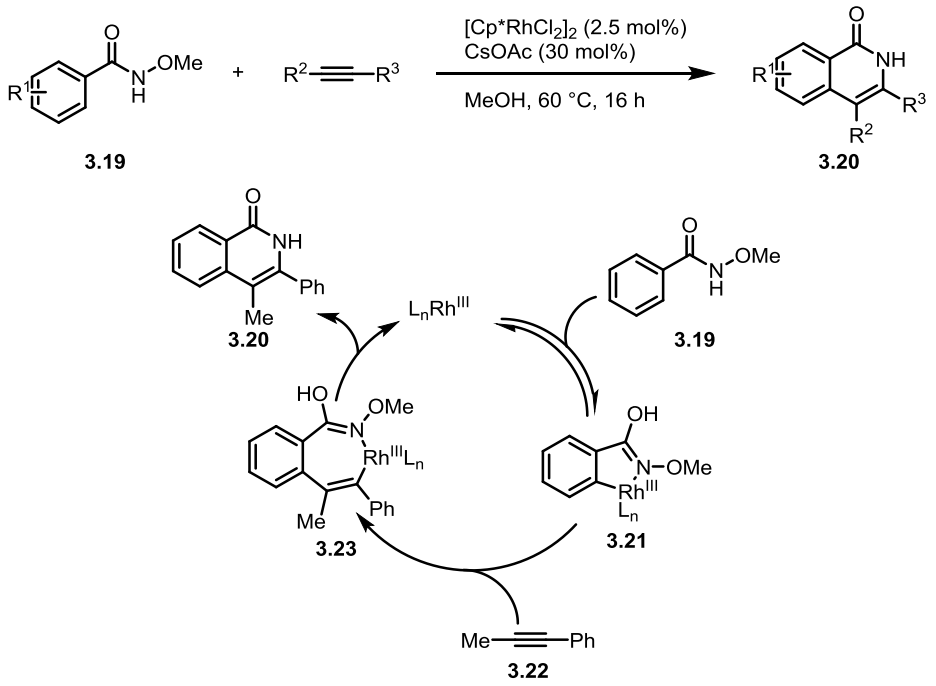
The internal oxidant can oxidise the catalyst at different points of the catalytic cycle, as demonstrated by the contrasting reports of Hartwig,[182] and Guimond and Fagnou.[184] In

Hartwig's intramolecular amination reaction in which an acyl oxime acts as the oxidising directing group, the first step of the reaction is the oxidative addition of Pd(0) into the N–O oxime bond (*Scheme 3.07*). Following tautomerisation of imine **3.15** to enamide **3.16**, C–H activation gives palladacycle **3.17**. Reductive elimination then gives indole **3.14** and Pd(0). The N–O bond cleavage was postulated to be the first step in the reaction mechanism after isolating analogous reaction intermediate **3.18** in which Pd(0) had undergone oxidative addition into the N–O bond of the corresponding acyl oxime.



Scheme 3.07. Oxime ester as an oxidising directing group

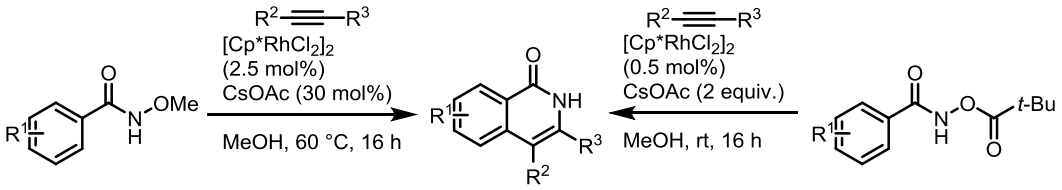
In contrast, Guimond and Fagnou propose catalyst oxidation in the last step of their rhodium-catalysed oxidative annulation work (*Scheme 3.08*). Initially, C–H functionalisation of *N*-methoxycarboxamide **3.19** leads to five-membered rhodacycle **3.21**. Following insertion of alkyne **3.22** to give seven-membered rhodacycle **3.23**, simultaneous N–O bond cleavage and reductive elimination of Rh(III) allows rhodium to maintain the +3 oxidation state required for catalytic activity.



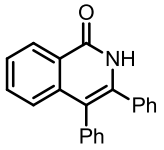
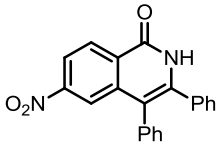
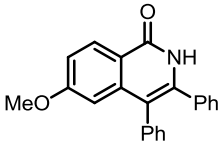
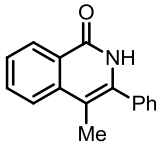
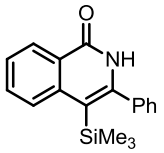
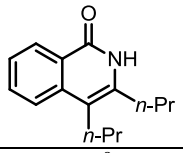
Scheme 3.08. Oxidative annulation using *N*-methoxycarboxamide as an oxidative directing group

Following the seminal reports on the use of *N*-methoxycarboxamide as a directing group, Guimond and Fagnou undertook a study of related directing groups.[185] After extensive optimisation, it was found that *N*-pivaloxyamide (pivaloxy = OCO_2t-Bu) was a superior directing group and facilitated oxidative annulation with dialkylalkynes—alkynes that had been largely unreactive using the *N*-methoxycarboxamide directing group (*Table 3.01*). Moreover, high yields could be achieved at room temperature with lower catalyst loadings. For alkylarylalkynes, the reaction was regioselective, with the aryl group being installed closest to nitrogen.

The mechanism of the reaction was thought to resemble that for *N*-methoxycarboxamide **3.19** (see *Scheme 3.08*) but in the case of *N*-pivaloxycarboxamide **3.24**, the final step of the reaction is assisted by the pivaloxy group (*Scheme 3.09*). DFT calculations provided support for a mechanism that involves reductive elimination (RE) of Rh(III) in rhodacycle **3.25** to give Rh(I) species **3.26**, followed by oxidative addition (OA) of Rh(I) into the N–O bond to give Rh(III) species **3.27**. Subsequent dissociation of species **3.27** then gives product **3.21** and returns the active Rh(III) catalyst to the catalytic cycle.

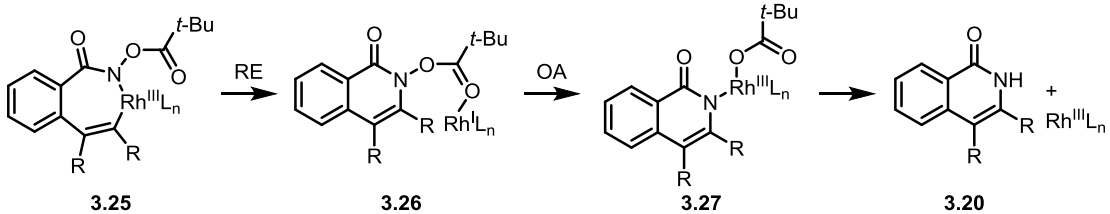


3.19 **3.20** **3.24**

Entry	Product	Yield from *N*-methoxycarboxamide **3.19** (%)	Yield from *N*-pivaloxycarboxamide **3.24** (%)
1		90	96
2		85	90
3		88	89
4		61	92
5		n/d	55
6		12[a]	70

[a] yield determined by ^{1}H NMR spectroscopy

Table 3.01. Comparison of *N*-methoxycarboxamide **3.19** with *N*-pivaloxycarboxamide **3.24**

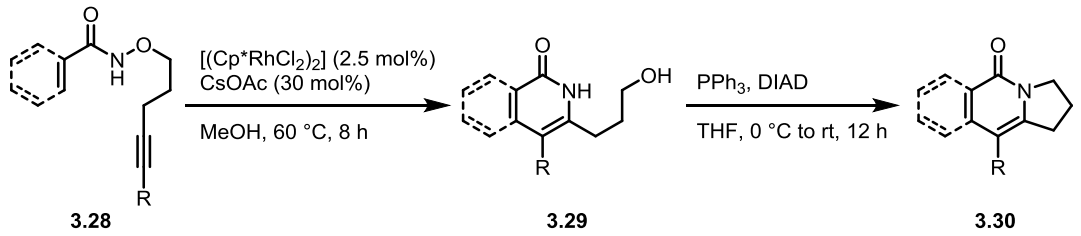


3.25 **3.26** **3.27** **3.20**

Scheme 3.09. Pivaloxy assisted reductive elimination of Rh(III)

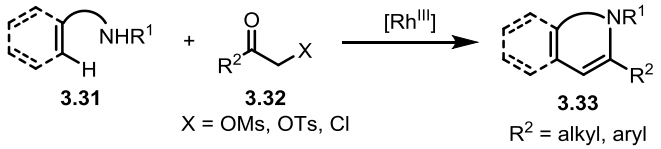
The reaction using *N*-pivaloxycarboxamide was also extended to terminal alkynes (which were subject to Glaser coupling[186-187] when using a Cu(II) salt as an external oxidant in previous systems) and alkenes.

The use of oxidising directing groups was elegantly demonstrated in the total synthesis of a series of natural products based on the indolizidine core (*Scheme 3.10*).[188] Using a tethered alkyne, carboxamide **3.28** underwent an intramolecular oxidative annulation to give isoquinolone derivative **3.29**, which was subsequently subjected to a Mitsunobu reaction to give indolizidine derivative **3.30**.



Scheme 3.10. Intramolecular oxidative annulation using an oxidising directing group

This redox-neutral strategy for the synthesis of heterocycles has since been employed by numerous groups, most recently by Glorius and co-workers who used *α*-OMs/-OTs/-Cl ketones **3.32** as oxidised alkyne equivalents (*Scheme 3.11*).[189]



Scheme 3.11. Recent redox-neutral strategy in oxidative annulation

Over the last decade or so, there has been an unprecedented amount of interest in C–H functionalisation and countless research groups are now investigating the field. A variety of substrates have been explored and the C–H functionalisation of organometallics, such as ferrocene, provides its own unique challenges.

3.1.2 Ferrocene

Ferrocene was first discovered in 1951 by Pauson and Kealy,[190] with the aromatic structure being independently determined the following year by Fischer and Pfab,[191] and Wilkinson *et al.*.[192] This groundbreaking discovery ultimately led to Fischer and Wilkinson being awarded the Nobel Prize in chemistry in 1973[193] and changed the face of modern organometallic chemistry, providing a deeper understanding of structure, bonding and reactivity. Since then, extensive research has been conducted into the unique structure and properties of ferrocene

and its derivatives, leading to applications of these compounds in numerous fields,[194-195] including catalysis,[196] electrochemistry, materials science, and bioorganometallic/medicinal chemistry.[197-198]

Compared to other aromatic compounds such as benzene, ferrocene has some remarkably different properties; for example, ferrocene undergoes electrophilic aromatic substitution 3×10^6 times faster than benzene, by virtue of the negatively charged cyclopentadienyl ligands.[199] However, the most obvious difference is the three-dimensional structure of ferrocene, which gives rise to planar chirality in 1,2- and 1,3-disubstituted ferrocenes (*Figure 3.01*). The R_p and S_p stereodescriptors are those given by Schlögl.[200]

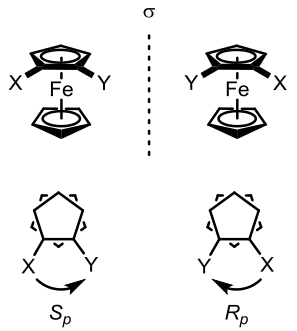


Figure 3.01. Planar chirality in 1,2-disubsituted ferrocenes (priority X > Y)

3.1.2.1 Applications

Ferrocene is an important rigid scaffold in chiral ligands such as Josiphos, Taniaphos, Mandyphos, and Xyliphos (*Figure 3.02*).[201] In addition to planar chirality, these ligands also contain central chirality.

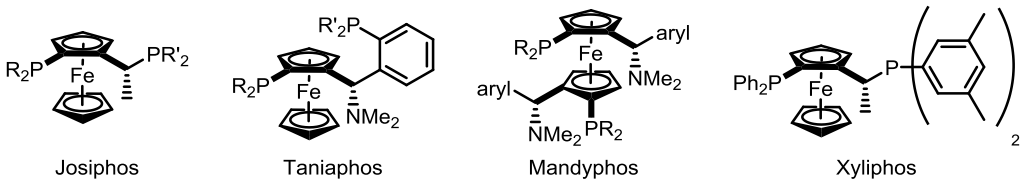
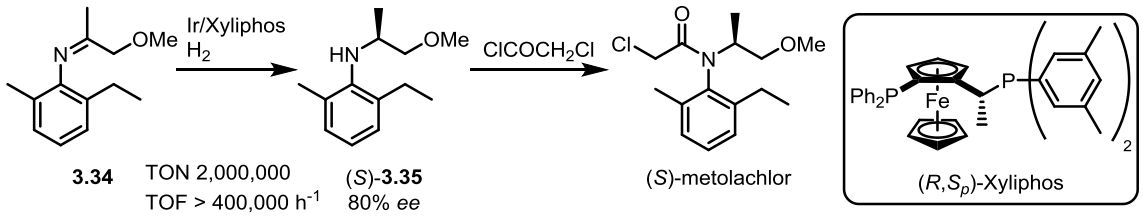


Figure 3.02. Selected ferrocene-based ligands

The Josiphos family of ligands have been used in countless asymmetric reactions; for example (R,S_p)-Xyliphos is used in the highly efficient catalytic enantioselective hydrogenation of imine **3.34**, a precursor in the synthesis of the herbicide (*S*)-metolachlor (*Scheme 3.12*). More than 10,000 tons of (*S*)-metolachlor are produced by

Ciba-Geigy/Syngenta every year.[202]



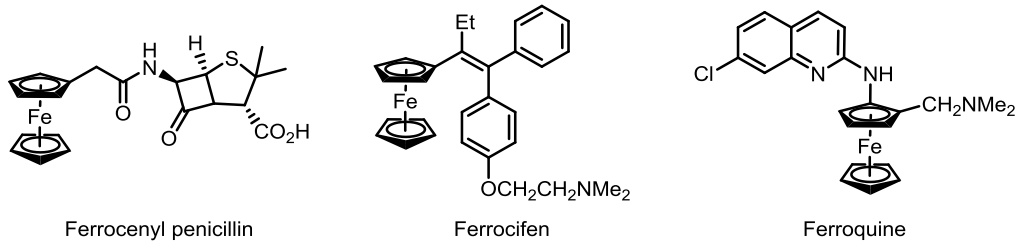
Scheme 3.12. Enantioselective synthesis of (*S*)-metolachlor

Owing to the low and readily reversible redox potentials of ferrocene, ferrocene and its derivatives are commonly used in electron transfer processes.[194, 203] Ferrocene undergoes a reversible one-electron oxidation to give ferrocenyl cation (*Equation 3.01*) and the redox couple is the recommended reference by IUPAC for reporting electrodes potentials measured in nonaqueous solvents.[204]

$$Fc^{+} + e^{-} \rightleftharpoons Fc \qquad E° = + 0.44 \text{ V (vs SCE in MeCN)}$$

Equation 3.01

The favourable redox properties, stability in aqueous aerobic media and the variety of derivatives that can be synthesised has made ferrocene and its derivatives good candidates for therapeutic agents. Ferrocene derivatives exhibit a wide range of biological activity and include the antibiotic ferrocenyl penicillin,[205] the cytotoxic ferrocifen[206] and the antimalarial ferroquine (*Figure 3.03*).[207]



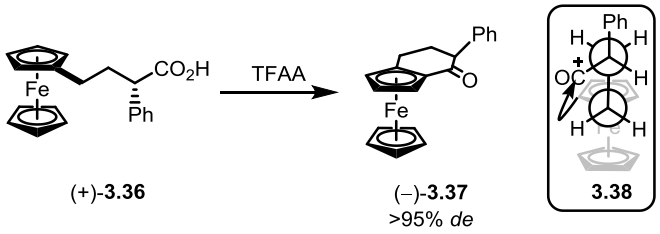
Ferrocenyl penicillin Ferrocifen Ferroquine

Figure 3.03. Examples of bioactive ferrocene complexes

3.1.2.2 Functionalisations

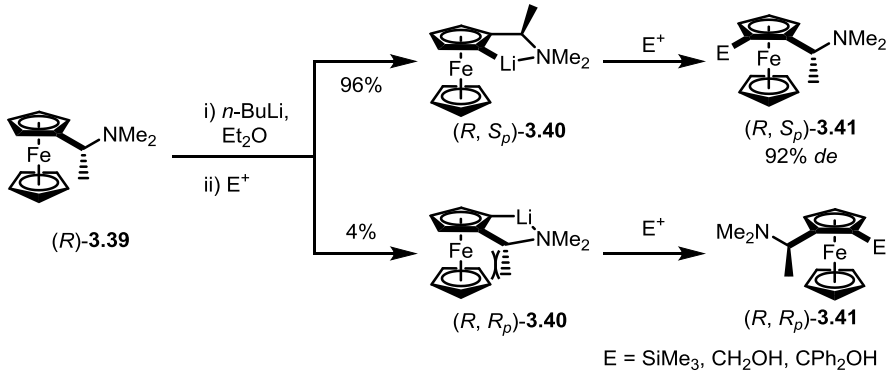
Ferrocene derivatives have been functionalised using a variety of strategies, mainly aromatic electrophilic substitution (for an example, see *Scheme 3.13*) and metallation reactions (for an example, see *Scheme 3.14*), and a recent review summarises the selective syntheses of planar chiral ferrocenes.[208] The first diastereoselective synthesis of a planar chiral ferrocene was

most likely the intramolecular Friedel-Crafts acylation of **3.36** in 1965 (*Scheme 3.13*).[209] Positioning the ferrocenyl and phenyl groups antiperiplanar results in the lowest energy intermediate **3.38**, leading to a highly diastereoselective cyclisation.



Scheme 3.13. Diastereoselective Friedel-Crafts acylation

The ferrocene ligands commonly used in asymmetric catalysis (see *Figure 3.02*) are generally accessed using a diastereoselective directed *ortho*-metallation (DoM) (*Scheme 3.14*). Metallation of enantioenriched Ugi's amine (*R*)-**3.39** preferentially gives organolithium (R,S_p)-**3.40**, which minimises the interaction between the α-methyl substituent and the ferrocene backbone. This can then be trapped with a range of electrophiles, including trimethylsilyl chloride, formaldehyde and benzophenone, to give (R,S_p)-**3.41** in 92% *de*.[210-211]



Scheme 3.14. Diastereoselective directed *ortho*-metallation

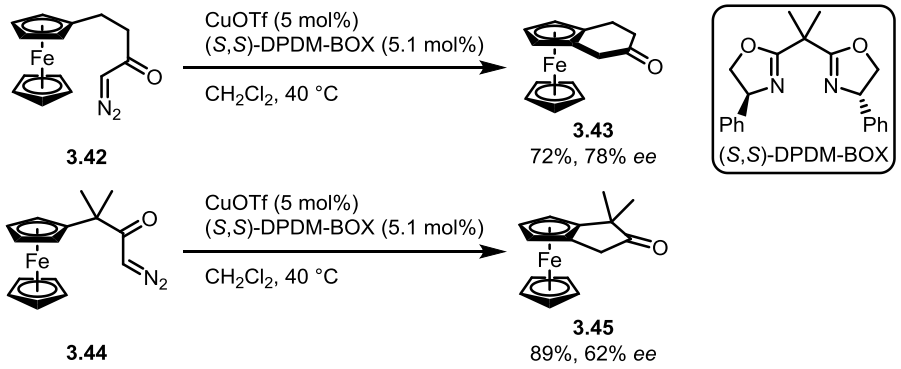
Metallation is undisputedly the most common method for the functionalisation of the ferrocene backbone, yet these reactions involve a stoichiometric amount of metal. Catalytic methods for the synthesis of ferrocene derivatives remains an underexplored area and recently there have been several reports that aim to address this.

3.1.2.2.1 Catalytic C–H Functionalisation

Although the C–H functionalisation of arenes is well established, ferrocene derivatives remain challenging substrates, likely owing to the unfavourable C–H deprotonation of the

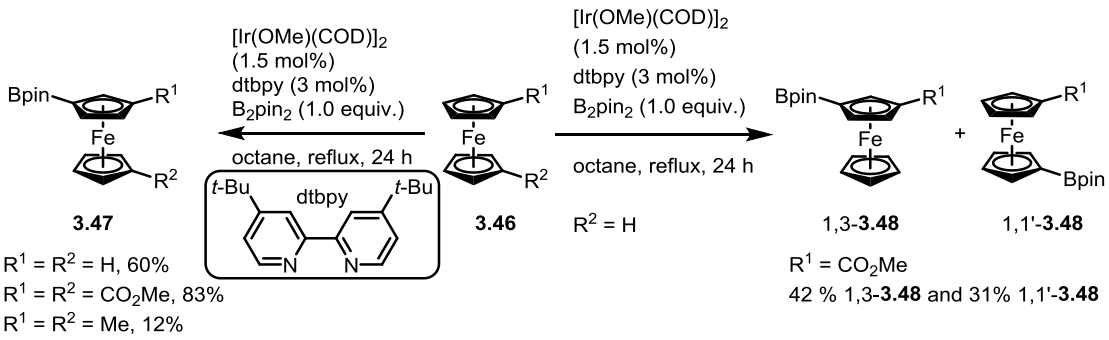
electron rich cyclopentadienyl rings. Nevertheless, there have been numerous reports on the synthesis of ferrocene metallacycles using stoichiometric metal.[212]

Siegel and Schmalz were the first to report the catalytic C–H functionalisation of ferrocene derivatives in 1997, using a copper-catalysed intramolecular carbene insertion into a Cp–H bond (*Scheme 3.15*).[213] Using a bis(oxazoline) (BOX) ligand, enantioselectivites up to 78% *ee* were obtained. However, substrate scope was limited owing to the intramolecular nature of the reaction.



Scheme 3.15. First catalytic C–H functionalisation of ferrocene

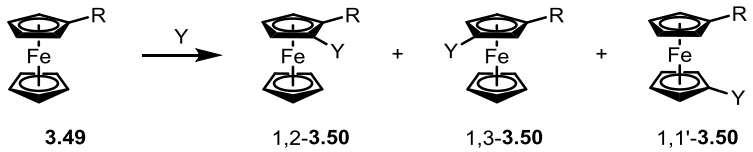
Another early example focussed on the iridium-catalysed borylation of ferrocene derivatives **3.46**.[214] However, regioselectivity was poor owing to the absence of a directing group and for monosubstituted ferrocenes, a mixture of 1,3- and 1,1'-disubsituted products was obtained. In addition, the reaction was only high yielding for ferrocene derivatives bearing electron-withdrawing substituents (*Scheme 3.16*).



Scheme 3.16. Iridium-catalysed borylation of ferrocene derivatives

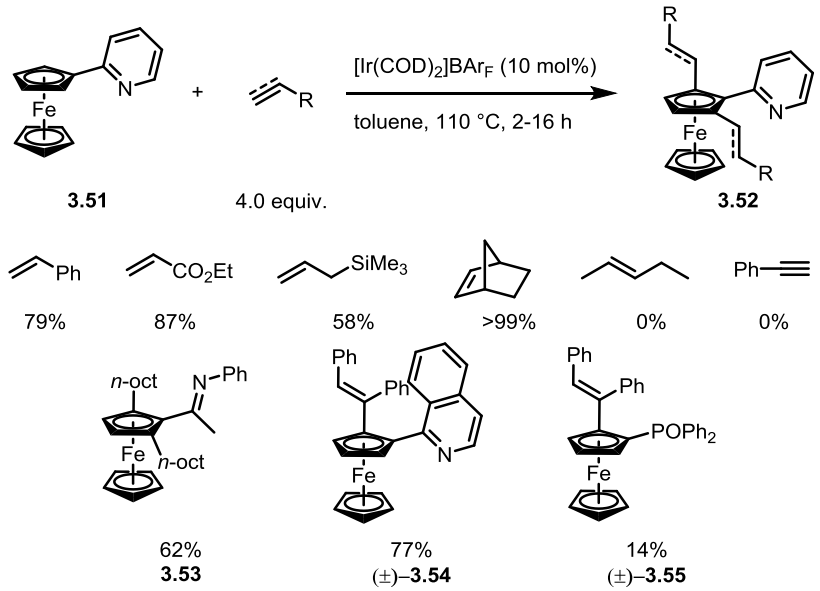
From the above example, it is obvious that the regioselectivity of the reaction can be complicated by the presence of the second cyclopentadienyl ring. Generally, for the

monofunctionalisation of a monosubstituted ferrocene e.g. **3.49**, three regioisomeric products are possible: 1,2-, 1,3- and 1,1'-disusbstituted ferrocenes **3.50** (*Scheme 3.17*).



Scheme 3.17. Regioselectivity for the functionalisation of monosubstituted ferrocene **3.49**

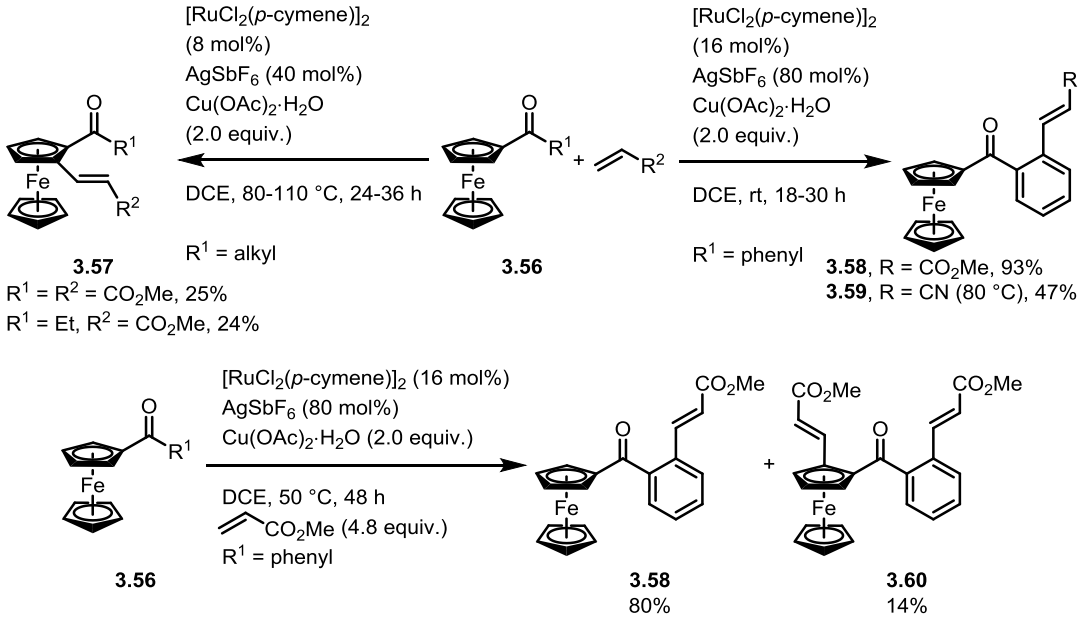
Directing groups can be used to control regioselectivity (see *section 3.1.1.1*); for example, Takebayashi and Shibata used iridium catalysis to effect the dialkenylation and dialkylation of ferrocene derivatives **3.51** using pyridine as a directing group (*Scheme 3.18*).[215] The scope of the directing group could also be extended to an imine, quinoline and phosphine oxide. With the use of the more sterically bulky quinoline or diphenylphosphine oxide directing group, selective monoalkenylation could be achieved to give racemic functionalised products (±)-**3.54** and (±)-**3.55**.



Scheme 3.18. Iridium-catalysed alkenylation and alkylation of ferrocene derivatives

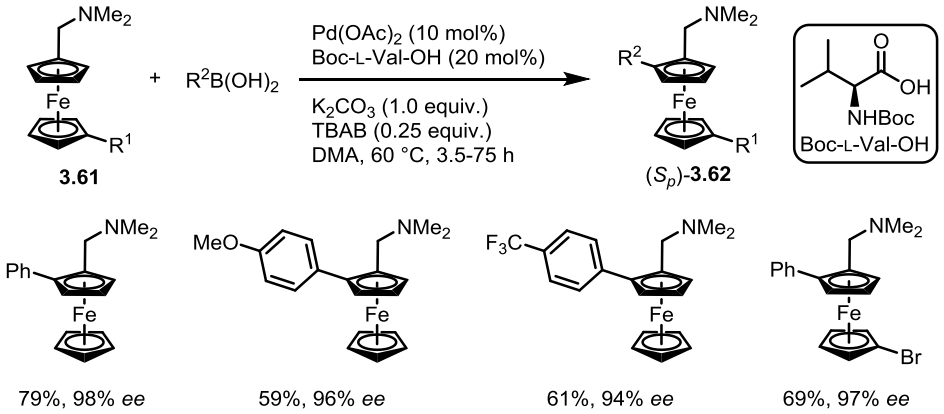
The alkenylation of ferrocenyl ketones **3.56** has also been achieved using ruthenium catalysis (*Scheme 3.19*),[216] with the ketone functionality acting as an efficient "weak" directing group. Interestingly, the regioselectivity of the alkenylation was dependent on the ketone substituent: for alkyl ketones, the ferrocene underwent selective alkenylation to give 1,2-disusbtituted ferrocenes **3.57**, whereas for aryl ketones alkenylation preferentially

occurred on the benzene ring to give ferrocenyl ketones **3.58** and **3.59**. When the reaction temperature was increased to 50 °C for aryl ketones, further alkenylation of intermediate **3.58** occurred on the ferrocene ring to give double alkenylation product **3.60**. These results suggest that the C–H functionalisation of ferrocenes derivatives is more challenging than for arenes.



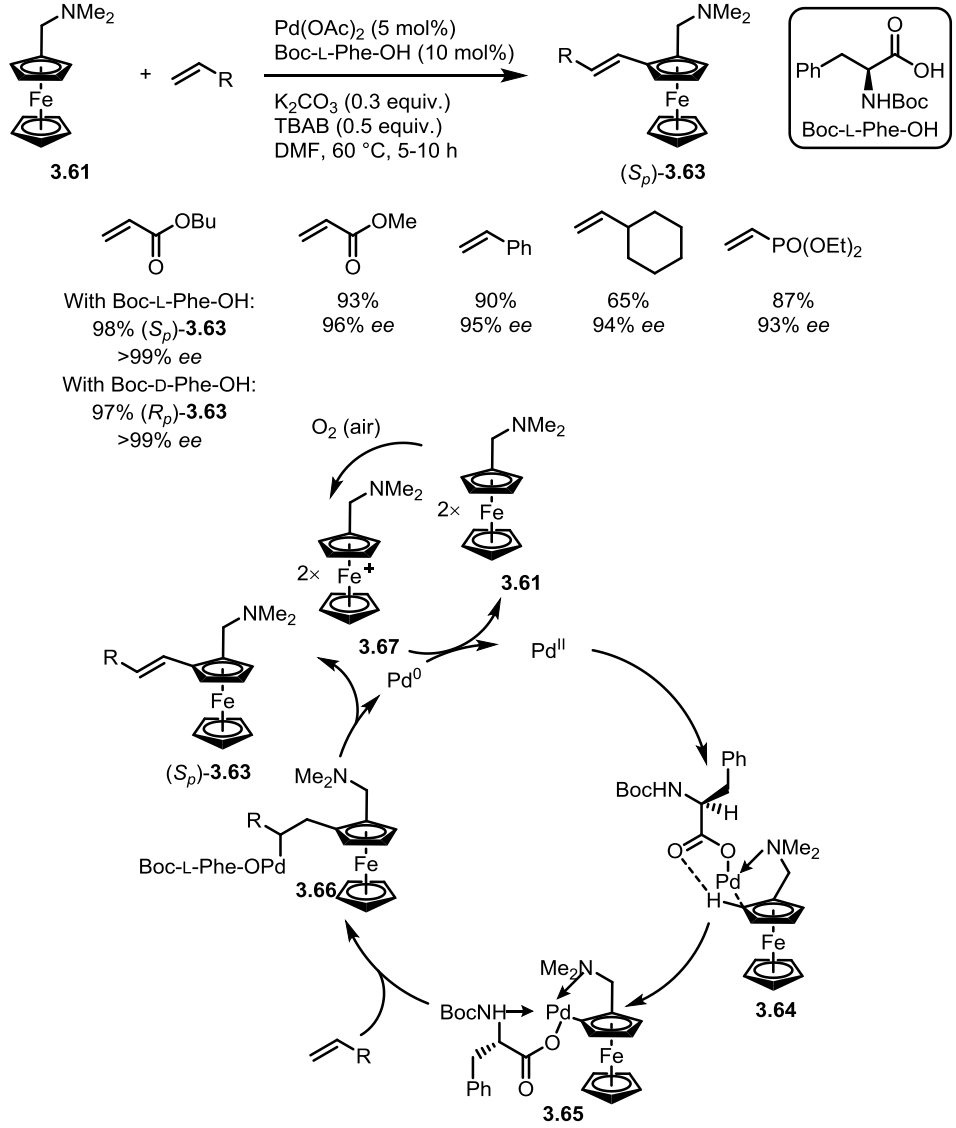
Scheme 3.19. Ruthenium-catalysed alkenylation of ferrocenyl ketones **3.56**

The enantioselective synthesis of planar chiral ferrocene derivatives has recently been achieved by You,[217] and Cui and Wu.[218] Both methodologies use a *N*,*N*-dimethylaminomethyl *ortho*-directing group and an enantiopure monoprotected amino acid ligand to differentiate between the two *ortho* protons. You and co-workers first reported the enantioselective arylation of ferrocene derivative **3.61** using arylboronic acids (*Scheme 3.20*). A range of aryl substituents were compatible and the products were consistently generated in excellent *ee*.[217]



Scheme 3.20. Enantioselective arylation of ferrocenyl amine **3.61**

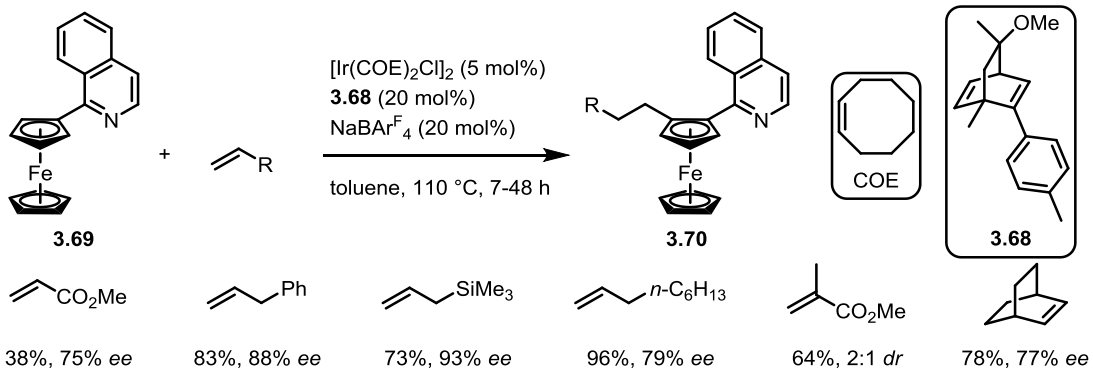
Cui and Wu subsequently reported the enantioselective alkenylation of the same ferrocene derivative **3.61** (*Scheme 3.21*).[218]



Scheme 3.21. Cui and Wu's alkenylation of *N*,*N*-dimethylaminomethyl ferrocene **3.61**

The Boc-L-Phe-OH ligand, coordinated to palladium in transition-state structure **3.64**, minimises the steric interactions between the ligand substituents and the ferrocene backbone thus selectively activating one proton *ortho* to the directing group to give intermediate **3.65**. Following coordination of the alkene and subsequent *syn*-carbopalladation to give ferrocene **3.66**, reductive elimination of the catalyst gives the alkene product (S_p)-**3.63** and Pd(0). Significantly, the substrate (**3.61**) acts as the oxidant for the regeneration of Pd(0) from Pd(II), following oxidation by air to form ferrocenium ion **3.67**. Two control experiments and HRMS evidence provided support that ferrocenium ion **3.67** acted as the terminal oxidant. Presumably, the arylation reaction described above also proceeds by this mechanism, with the substrate acting as the oxidant for Pd(0).[217]

Very recently, the first example of the enantioselective alkylation of ferrocene derivatives **3.69** was reported using iridium catalysis and a chiral diene ligand **3.68** (*Scheme 3.22*).[219] A range of alkenes were tolerated, although there were no examples of alkenes bearing electron-donating substituents. For styrene derivatives, the reaction was complicated by a mixture of linear and branched derivatives products (not shown).



Scheme 3.22. Enantioselective alkylation of (isoquinolin-1-yl)ferrocene **3.69**

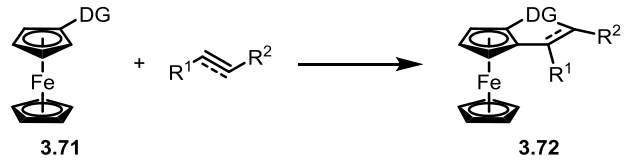
To summarise, the enantioselective arylation, alkenylation and alkylation of ferrocene derivatives have all recently been achieved, greatly contributing to the methods available for the synthesis of planar chiral ferrocenes.

3.1.3 Oxidative Annulation of Ferrocene Derivatives

Clearly, the C–H functionalisation of ferrocene derivatives is more challenging than for

arenes owing to the unique properties of ferrocene and consequently, the yields and regioselectivities of these reactions are often lower. However, the inherent planar chirality of 1,2- and 1,3-disusbtituted ferrocene derivatives and their diverse applications makes the stereoselective synthesis of these compounds a worthwhile pursuit.

At the onset of this work, there were no reports on the oxidative annulation of ferrocene derivatives **3.71** to generate 1,2-disusbstituted ferrocenes **3.72** (*Scheme 3.23*). Using this strategy, regioselectivity would be controlled, as ring closure would occur *ortho* to the directing group. There would also be the possibility to develop an enantioselective method to generate 1,2-disusbstituted planar chiral ferrocenes.

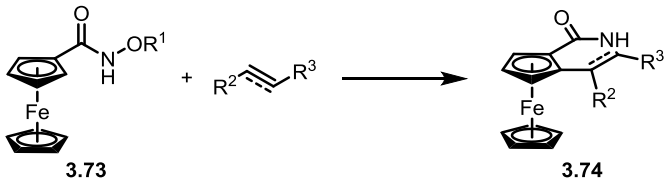


Scheme 3.23. Oxidative annulation of ferrocene derivative **3.71**

3.2 Results and Discussion

3.2.1 Aims

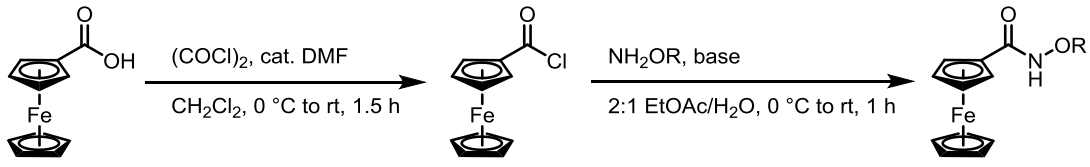
With the aim of exploring the oxidative annulation of ferrocenes, *N*-alkoxyferrocenecarboxamide substrates **3.73** were investigated (*Scheme 3.24*). Using an *N*-alkoxycarboxamide directing group would negate the use of an external oxidant, thus allowing the development of a mild and general protocol as shown by Guimond and Fagnou in the highly successful synthesis of isoquinolones (see *section 3.1.1.1*).[184-185]



Scheme 3.24. Oxidative annulation of *N*-alkoxyferrocenecarboxamide **3.73**

3.2.2 Substrate Synthesis

N-Methoxy- **3.77** and *N*-pivaloxycarboxamide **3.78**, containing the two directing groups used by Guimond and Fagnou,[184-185] were synthesised from commercially available ferrocenecarboxylic acid **3.75** *via* acid chloride **3.76** (*Table 3.02*).



3.75 **3.76** **3.73**

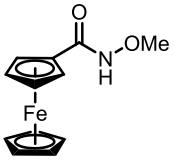
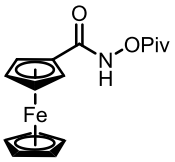
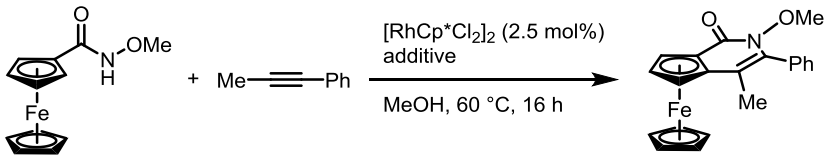
Entry	Amine	Base	Product	Yield (%)
1	$NH_2OMe \cdot HCl$	K_2CO_3	 **3.77**	88
2	$NH_2OPiv \cdot TfOH$	Na_2CO_3	 **3.78**	43

Table 3.02. Synthesis of substrates **3.77** and **3.78**

3.2.3 Initial Results with Rhodium

Inspired by the work of Fagnou and co-workers on the rhodium-catalysed synthesis of isoquinolones,[184] the reaction conditions used in this report were directly applied to *N*-methoxycarboxamide **3.77** and 1-phenyl-1-propyne **3.22** (*Table 3.03, entry 1*). A 30% conversion of amide **3.77** into annulation product **3.79** was observed over 16 h, but in contrast to the transformation reported by Fagnou, the product contained an intact N–O bond. Since the observed 30% conversion matched the cesium acetate loading, the reaction was repeated with 1.1 equivalents of cesium acetate, but no improvement in conversion was observed (*entry 2*). It was clear that N–O bond cleavage was not responsible for catalyst turnover and so it was reasoned that another species present in the reaction was performing this function. As the reaction was conducted in an open flask, it was postulated that air could be acting as the oxidant to regenerate the active catalyst. As a control experiment, the reaction was performed in degassed methanol under an atmosphere of nitrogen and no product was detected (*entry 3*), thus supporting the hypothesis that oxygen was responsible for catalyst turnover.



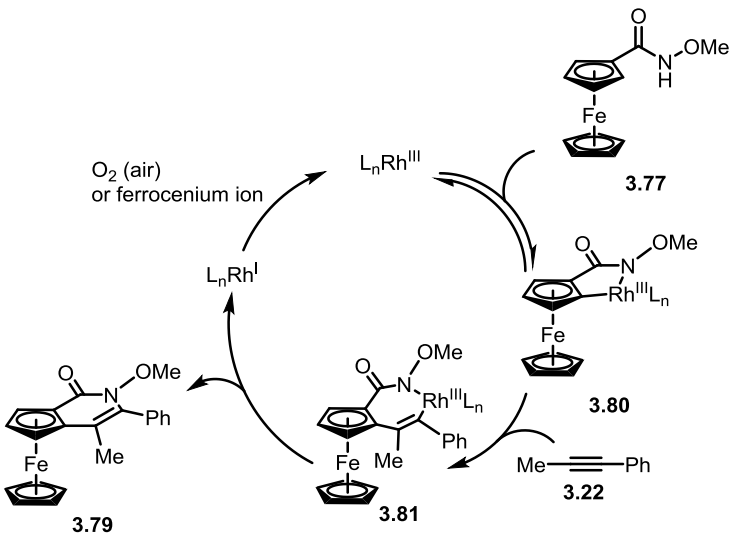
3.77 **3.22** **3.79**

Entry	Additive	Amount	Conversion (%)[a]
1	CsOAc	30 mol%	30
2	CsOAc	1.1 equiv.	30
3	CsOAc	30 mol%	0[b]
4	-	-	0
5	NaOAc	30 mol%	35
6	KOAc	30 mol%	30
7	NaOAc	2.1 equiv.	22
8	CF_3CO_2Na	2.1 equiv.	no reaction
9	NaOAc	1.1 equiv.[c]	22
10	K_2CO_3	2.0 equiv.	trace
11	K_2CO_3, $MesCO_2H$	2.0 equiv., 30 mol%	trace
12	K_2CO_3, PivOH	2.5 equiv., 30 mol%	trace
13	K_2CO_3, AcOH	2.5 equiv., 30 mol%	trace
14	K_2CO_3, NaOAc	2.5 equiv., 30 mol%	trace
15	KOPiv, NaOAc	1.1 equiv., 30 mol%	trace
16	KOPiv	1.1 equiv.	trace
17	NaOH	1.1 equiv.	trace
18	NaOMe	1.1 equiv.	trace
19	NaOBn	1.1 equiv.	trace

[a] conversion determined by ^{1}H NMR spectroscopy based on remaining substrate
[b] reaction performed in degassed methanol under an atmosphere of nitrogen
[c] added over 1 h

Table 3.03. Additive screening

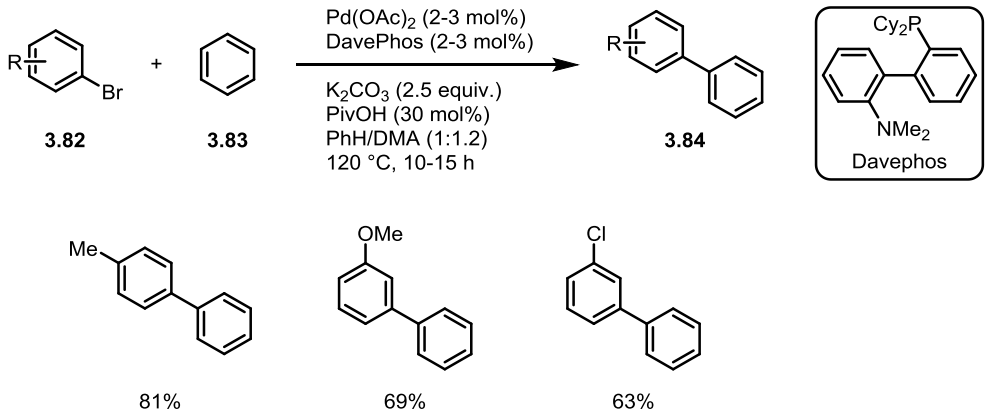
Based on the mechanism for the oxidative annulation of *N*-methoxycarboxamide **3.19** (see *Scheme 3.08*), the only difference with the ferrocene analogue **3.77** is the final step. Instead of the N–O bond cleaving to regenerate free Rh(III), the N–O bond remains intact and after reductive elimination to give product **3.79** and Rh(I), oxygen in the air oxidises Rh(I) back to Rh(III) (*Scheme 3.25*).



Scheme 3.25. Proposed mechanism for oxidative annulation of *N*-methoxycarboxamide **3.77**

In an attempt to improve conversion, different additives were screened. No conversion to annulation product **3.79** was observed when the reaction was performed without an additive (*entry 4*), highlighting the crucial role that an additive plays in this reaction. Disappointingly, conversions similar to the 30% obtained with cesium acetate were observed with sodium and potassium acetate—35% and 30% respectively (*entries 5 and 6*). Since two protons are removed per molecule of starting material, the reaction was also performed using 2.1 equivalents of NaOAc, but the conversion was again poor at only 22% (*entry 7*). Replacing sodium acetate with the less basic sodium trifluoroacetate (by virtue of the electron-withdrawing trifluoro moiety) suppressed the reaction altogether (*entry 8*), revealing that the reaction is highly sensitive to the basicity of the additive.

In 2006, Fagnou and Lafrance reported the palladium-catalysed arylation of benzene **3.83** with aryl bromides **3.82**, which used stoichiometric potassium carbonate and catalytic pivalic acid additives (*Scheme 3.26*).[220] Stoichiometric potassium carbonate alone gave <5% conversion and it was only by using stoichiometric potassium carbonate in conjunction with catalytic pivalic acid that 100% conversion was achieved. It was reasoned that pivalic acid acted as a proton shuttle between benzene and potassium carbonate thus facilitating the reaction. Furthermore, it was crucial for potassium carbonate to remain insoluble in the reaction, as excess carboxylate base was found to interfere with reactivity.



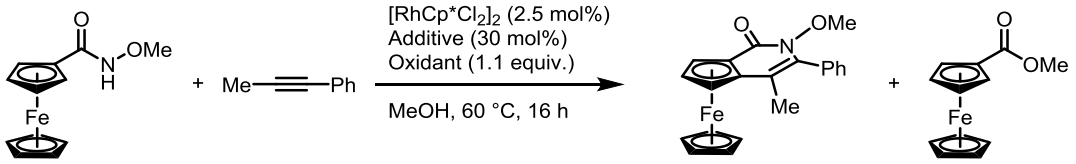
Scheme 3.26. Benzene arylation using catalytic pivalic acid

With this observation in mind, 1.1 equivalents of sodium acetate were added over one hour to minimise the concentration of acetate present at any one time, but this only gave a conversion of 22% (*entry 9*). Therefore, taking inspiration directly from Fagnou and Lafrance's arylation work, the reaction was performed with potassium carbonate (*entry 10*), and potassium carbonate in combination with three different organic acids (*entries 11-13*); no product was observed using any of these conditions. Based on the success of sodium acetate as an additive, the reaction was performed using catalytic sodium acetate and stoichiometric potassium carbonate (*entry 14*), in the hope that the acetic acid generated *in situ* would be deprotonated by K_2CO_3, again minimising the concentration of acetate present in solution. Unfortunately no product was observed in this reaction, or when potassium carbonate was replaced with alternative base potassium pivalate (*entry 15*). Finally, four different bases were screened based on their range of basicity (*entries 16-19*) but no product was observed in any case.

Due to the marginally higher conversion obtained using sodium acetate compared with cesium acetate, combined with the lower cost of sodium acetate, the majority of future experiments were performed using sodium acetate as an additive.

In an attempt to improve the turnover of the catalyst and hence the yield of the reaction, a range of oxidants were screened (*Table 3.04*). $Cu(OAc)_2$ and $K_2S_2O_8$, oxidants commonly used in C–H activation, both appeared to suppress the reaction (*Table 3.04*, *entries 1 and 2*). Interestingly, when Ag_2O was employed in the reaction, no annulation product **3.79** was

detected and a product with NMR spectroscopic data consistent with methyl ester **3.85** was isolated (*entry 3*). Suspecting that methyl ester **3.85** could have arisen through nucleophilic attack of methanol on an activated molecule of amide **3.77**, the reaction was repeated in different solvents. However all solvents gave methyl ester **3.85**, suggesting that it originates from an intramolecular rearrangement of substrate **3.77**. Of the oxidants screened, only oxygen facilitated the annulation reaction, albeit in low yield (*entry 4*). Two further oxidants were investigated, 1,4-benzoquinone and benzoyl peroxide, but no product was detected (*entries 5 and 6*). From the proposed catalytic cycle (see *Scheme 3.25*) Rh(I) needs to be oxidised to Rh(III), yet puzzlingly oxidising conditions seemed detrimental to the reaction.

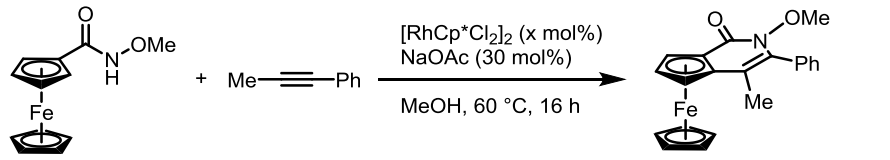


Entry	Additive	Oxidant	Conversion (%)[a]
1		$Cu(OAc)_2$[b]	0
2	CsOAc	$K_2S_2O_8$	0
3		Ag_2O[c]	37% **3.85**[d]
4		O_2	19% **3.79**
5	NaOAc	1,4-benzoquinone	0
6		benzoyl peroxide	0

[a] conversion determined by ^{1}H NMR spectroscopy based on remaining substrate
[b] 2.2 equiv.
[c] methyl ester **3.85** also obtained in *t*-AmOH, THF and DCE
[d] isolated yield

Table 3.04. Screening of oxidants

Catalyst loading and conversion should be directly proportional if catalyst turnover was a problem, but unfortunately this was not the case and similar conversions were achieved with three different catalyst loadings (*Scheme 3.27*). It is important to note that all three reactions were performed in the same volume of solvent so the concentration of catalyst would be different in each, but nevertheless these results suggested that another variable was limiting the reaction.

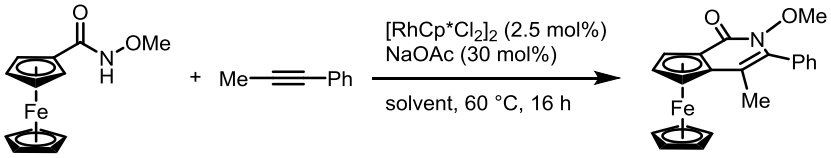


3.77 **3.22** **3.79**

2.5 mol% Rh, 27% conversion
5 mol% Rh, 32% conversion
10 mol% Rh, 27% conversion

Scheme 3.27. Investigating catalyst turnover

The choice of solvent for the reaction was also investigated, but very little or no product was observed when the reaction was conducted in any solvent other than MeOH (*Table 3.05*). Both polar solvents, including alternative alcohols ethanol and *t*-butanol, and non-polar solvents were ineffective for the reaction. Methanol was also added as an additive to a reaction conducted in THF, but no reaction occurred (*entry 8*).



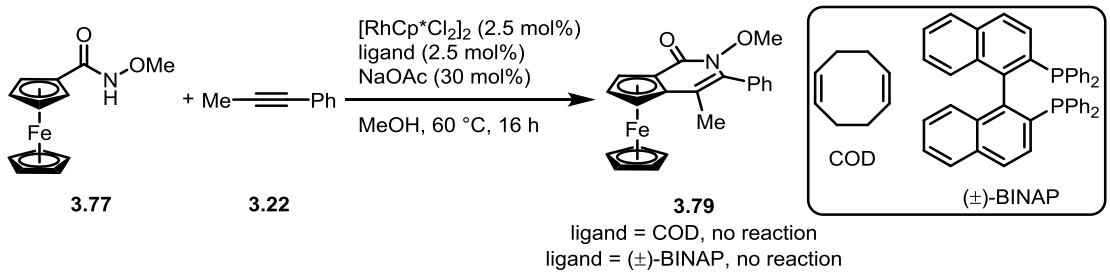
3.77 **3.22** **3.79**

Entry	Solvent	Conversion (%)[a]
1	MeOH	35
2	EtOH	trace
3	*t*-BuOH	no reaction
4	MeCN	9
5	PhMe	trace
6	$CHCl_3$	no reaction
7	THF	no reaction
8	THF, MeOH (2.1 equiv.)	no reaction

[a] conversion determined by ^{1}H NMR spectroscopy based on remaining substrate

Table 3.05. Solvent screening

The inclusion of ligands is sometimes critical for a reaction to succeed, as they change the electronic and steric nature of the catalyst and can stabilise active catalytic species. To this end, the reaction was performed using the diene 1,5-cyclooctadiene (COD), which is a common ligand used in rhodium catalysis, and racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) (*Scheme 3.28*). Unfortunately, no reaction occurred with either ligand, suggesting that additional rhodium ligands are detrimental to reactivity.

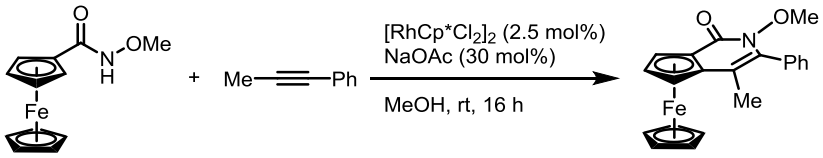


3.77 **3.22** **3.79**

ligand = COD, no reaction
ligand = (±)-BINAP, no reaction

Scheme 3.28. Reactions conducted with ligands

The reaction was also conducted at room temperature, in an attempt to prolong the life of the catalyst and thus increase the yield of the reaction (*Scheme 3.29*). A lower conversion was in fact observed, suggesting a higher temperature is required for the reaction to overcome the activation energy for the reaction.

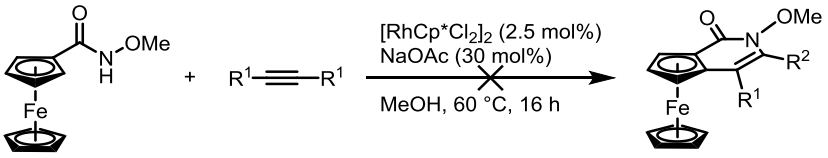


3.77 **3.22** **3.79**

13% conversion

Scheme 3.29. Reaction conducted at room temperature

In addition to 1-phenyl-1-propyne **3.22**, dialkylalkyne 4-octyne **3.86** and diarylalkyne diphenylacetylene **3.87** were screened in the reaction (*Scheme 3.30*). Only a trace amount of annulation product was observed when 4-octyne **3.86** was used, and no reaction occurred with diphenylacetylene **3.87**.

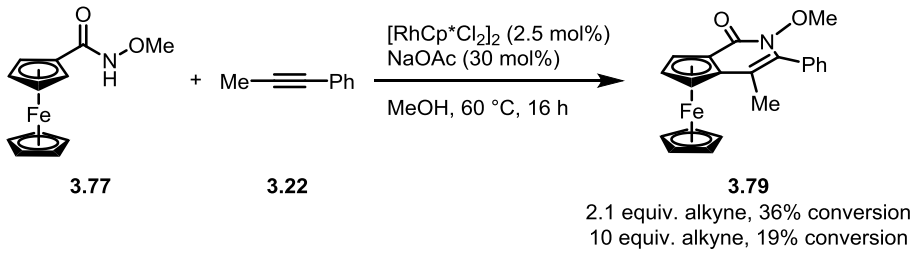


3.77 **3.88**

3.86 $R^1 = R^2 = n$-Pr
3.87 $R^1 = R^2$ = Ph

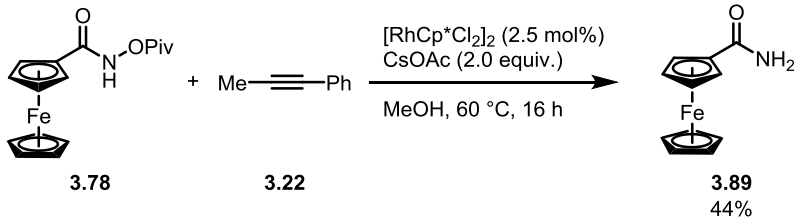
Scheme 3.30. Screening 4-octyne and diphenylacetylene

Reverting to 1-phenyl-1-propyne **3.22**, alkyne stoichiometry was then investigated. It was hoped that increasing the number of equivalents would improve the yield of product **3.79** (*Scheme 3.31*). Increasing the alkyne stoichiometry from 1.1 to 2.1 equivalents did not affect the conversion (35% for 1.1 compared to 36% for 2.1), but further increasing this to 10 reduced the conversion to 19%.



Scheme 3.31. Screening number of alkyne equivalents

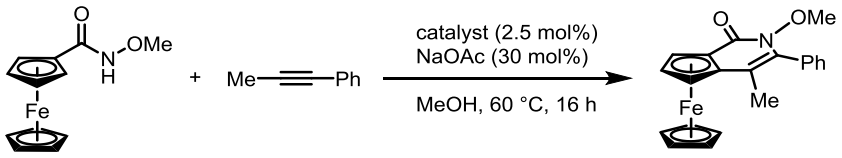
Finally, the oxidative annulation of *N*-pivaloxycarboxamide **3.78** was attempted using the conditions developed by Guimond and Fagnou for the oxidative addition of the analogous *N*-pivaloxycarboxamide **3.24** (see *Table 3.01*)[185] (*Scheme 3.32*). In contrast to Fagnou's findings, *N*-pivaloxycarboxamide **3.78** did not prove a superior substrate to *N*-methoxycarboxamide **3.77**, and instead the N–O bond of the substrate cleaved to give free amide **3.89** in 44% isolated yield with no accompanying annulation product.



Scheme 3.32. Reaction of *N*-pivaloxycarboxamide **3.78**

3.2.4 Initial Results with Palladium

After investigating a wide range of different reaction conditions with $[RhCp^*Cl_2]_2$ and achieving a maximum conversion of about 35%, alternative metal catalysts were screened, focusing initially on Ru(II), Ir(III), Rh(I) and Pd(II) sources (*Table 3.06*). No reaction was observed with $[RuCl_2(p\text{-cymene})]_2$ and alternative rhodium catalysts $[Rh(COD)Cl]_2$ and $[Rh(COD)_2]^+BF_4^-$ (both Rh(I) sources in comparison to Rh(III) source $[RhCp^*Cl_2]_2$ previously investigated) (*Table 3.06, entries 1-3*). Earlier reactions with COD and BINAP ligands had proven unsuccessful so it perhaps not surprising that both Rh(I) sources, which contain COD, did not catalyse the reaction (see *Scheme 3.28*). $[IrCp^*Cl_2]_2$, a catalyst electronically similar to $[RhCp^*Cl_2]_2$, was also ineffective (*entry 4*).



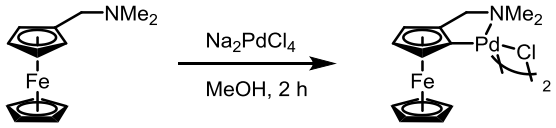
3.77 **3.22** **3.79**

Entry	Catalyst	Conversion (%)[a]
1	$[RuCl_2(p\text{-cymene})]_2$[b]	no reaction
2	$[Rh(COD)Cl]_2$	no reaction
3	$[Rh(COD)_2]^+BF_4^-$	no reaction
4	$[IrCp^*Cl_2]_2$[c]	no reaction
5	Na_2PdCl_4[d,e]	42
6	Na_2PdCl_4[d,e,f]	trace

[a] conversion determined by ^1H NMR spectroscopy based on remaining substrate
[b] CsOAc (30 mol%) used as additive
[c] 2.1 equiv. NaOAc
[d] 10 mol% Na_2PdCl_4
[e] diphenylacetylene **3.87** used instead of 1-phenyl-1-propyne **3.22**
[f] no additive

Table 3.06. Screening of other metal catalysts

Inspired by the 1975 paper by Gaunt and Shaw,[221] which reported the stoichiometric cyclopalladation of *N*,*N*-dimethylaminomethyl ferrocene **3.61** using Na_2PdCl_4 and sodium acetate (*Scheme 3.33*), the same catalyst was screened in the oxidative annulation of *N*-methoxycarboxamide **3.77** and pleasingly, Na_2PdCl_4 gave rise to a 42% conversion (*entry 5*). Since Shaw had only observed successful cyclopalladation in the presence of sodium acetate, the reaction was repeated in the absence of sodium acetate and only a trace amount of product was formed (*entry 6*). Again, these results serve to highlight the crucial role that an additive can play in C–H functionalisation.

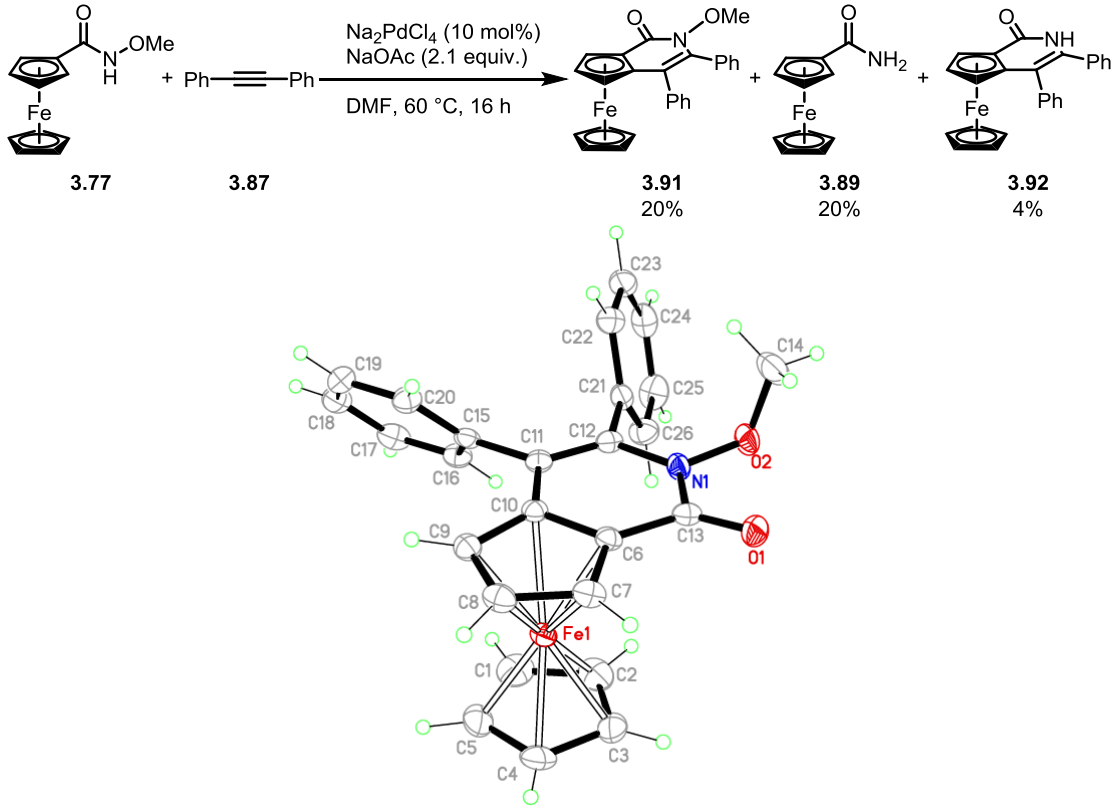


3.61 **3.90**
no additive: 0%
NaOAc (1.0 equiv.): 84%

Scheme 3.33. C–H activation using Na_2PdCl_4

It was subsequently found that the oxidative annulation of ferrocenecarboxamide **3.77** could also be performed in DMF, and using diphenylacetylene **3.87** as the alkyne, a 20% isolated yield of annulation product **3.91** was obtained (*Scheme 3.34*) (in this experiment and in all future experiments, 2.1 equivalents of sodium acetate were used, as two protons per

molecule of substrate are formally removed). Interestingly, free amide **3.89** was also obtained in 20% yield alongside 4% of the annulation product **3.92**, in which the N–O bond had cleaved. Annulation product **3.91** was crystalline and X-ray crystallography was used to unambiguously confirm the structure.

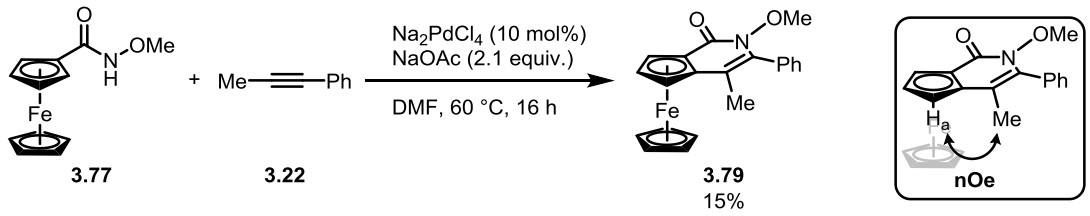


Scheme 3.34. Oxidative annulation of **3.79** with diphenylacetylene **3.87** and X-ray crystal structure of **3.91**

It is interesting to contrast the oxidative annulation of *N*-methoxycarboxamide **3.77** with diphenylacetylene **3.87** using rhodium and palladium catalysis. No reaction was observed with this alkyne using $[RhCp^*Cl_2]_2$, yet a 20% yield of product **3.91** was isolated using Na_2PdCl_4. Pleasingly, Na_2PdCl_4 also catalysed the oxidative annulation of *N*-methoxycarboxamide **3.77** with 1-phenyl-1-propyne **3.22** (*Scheme 3.35*), but in contrast to the 20% isolated yield of annulation product **3.91** obtained with diphenylacetylene **3.87**, a lower yield of 15% of the analogous product **3.79** was isolated.

The lower reactivity of alkylarylalkynes compared with diarylalkynes and the regioselectivity of the reaction was consistent with the literature,[185] with the aryl substituent

being incorporated closest to nitrogen; through 1D nOe analysis of the product, a mutual enhancement was observed between the vinyl methyl protons and H_a.



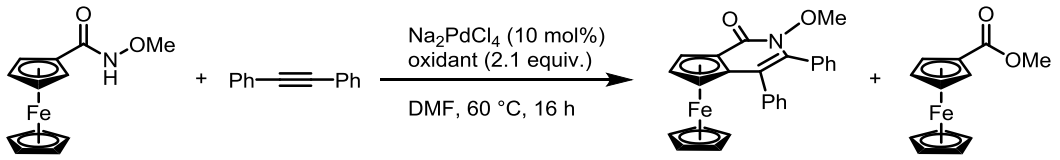
3.77 **3.22** **3.79** 15%

Scheme 3.35. Oxidative annulation of *N*-methoxycarboxamide **3.77** with 1-phenyl-1-propyne **3.22**

Given that both product **3.91** and free amide **3.89** were isolated in equal yield using diphenylacetylene **3.87** (see *Scheme 3.34*), it was speculated that the N–O bond of the substrate itself was cleaving and turning over the catalyst. Therefore, in an effort to prevent this sacrificial loss of substrate, a range of oxidants were screened (*Table 3.07*). AcNHOMe and BocNHOPiv were chosen to resemble substrate **3.77** in the hope that the N–O bond of the additives would preferentially cleave over the equivalent bond in the substrate (*Table 3.07, entries 1 and 2*), but only a 12% yield by ^{1}H NMR spectroscopy was obtained using AcNHOMe and no reaction was observed with BocNHOPiv. Both AcNHOMe and BocNHOPiv could potentially act as polydentate ligands for palladium so it is perhaps not surprising that the reactions were low yielding.

Next, oxidants commonly used in C–H activation were screened (*entries 3-9*) and all either prevented the reaction, gave product **3.77** in low yield or converted *N*-methoxycarboxamide **3.77** into methyl ester **3.85**, which had previously been observed when using silver oxidants with rhodium catalysis (see *Table 3.04*).

Finally, catalytic ferrocene was screened as an oxidant (*entry 10*) in the hope of using the *in situ* generated ferrocenium ion as an oxidant, similar to that observed by Wu (see *Scheme 3.21*).[218] However, no improvement in yield was observed and annulation product **3.91** was observed in 25% yield by ^{1}H NMR spectroscopy.



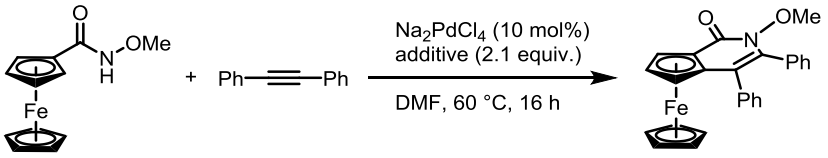
3.77 **3.87** **3.91** **3.85**

Entry	Oxidant	Yield (%)[a]
1	AcNHOMe	12
2	BocNHOPiv	no reaction
3	$Cu(OAc)_2$	9 + **3.85**
4	$(BzO)_2$	no reaction
5	$PhI(OAc)_2$	**3.85**
6	$K_2S_2O_8$	no reaction
7	AgOAc	**3.85**
8	NFSI	no reaction
9	benzoquinone	14
10	ferrocene[b]	25

[a] yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard
[b] 10 mol% under air

Table 3.07. Oxidant screening

Next, additives were screened (*Table 3.08*). No reaction occurred in the absence of an additive, but a 37% yield by ^{1}H NMR spectroscopy was obtained using 2.1 equivalents of sodium acetate (*Table 3.08, entries 1 and 2*).



3.77 **3.87** **3.91**

Entry	Oxidant	Yield (%)[a]
1	-	no reaction
2	NaOAc	37
3	KOAc	no reaction
4	CsOAc	no reaction
5	K_2CO_3	no reaction
6	NaOAc + TBAB (1.0 equiv.)	38
7	KOPiv	no reaction
8	K_2CO_3 (2.5 equiv.) + PivOH (0.3 equiv.)	no reaction

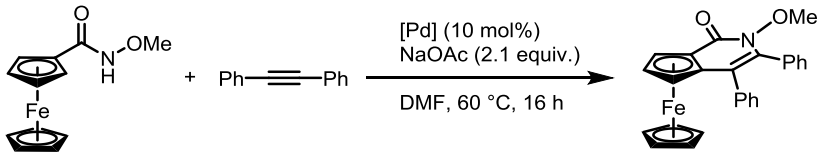
[a] yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard

Table 3.08. Additive screening

In contrast to the screening performed with rhodium, no reaction occurred when either potassium or cesium acetate was used (*entries 3-4*). The addition of potassium carbonate did not facilitate the reaction and the addition of TBAB, which has been shown to increase the yield of some reactions,[217] did not have a beneficial effect with only a modest 38% yield by

^{1}H NMR spectroscopy observed (e*ntries 5 and 6*). No reaction was observed when either potassium pivalate or the combination of potassium carbonate and pivalic acid was screened (*entries 7 and 8*).

A variety of palladium sources were next screened and interestingly palladium acetate, a common C–H functionalisation catalyst, only gave the product in 1% yield by ^{1}H NMR spectroscopy (*Table 3.09*, *entry 1*). Switching the ligand to trifluoroacetate only gave a small increase in yield to 4% (*entry 2*). Pleasingly, palladium chloride catalysed the reaction successfully and a 28% yield was observed (*entry 3*). Related palladium sources $Pd(PPh_3)_2Cl_2$ and $Pd(MeCN)_2Cl_2$ also facilitated the reaction and yields of 23% and 37% respectively were recorded (*entries 4 and 5*). Comparing the yields by ^{1}H NMR spectroscopy obtained with alternative palladium sources to the one obtained with Na_2PdCl_4, 37% (*entry 6*), no significant improvement had been made and it was decided to continue screening using Na_2PdCl_4.



3.77 **3.87** **3.91**

Entry	[Pd]	Yield (%)[a]
1	$Pd(OAc)_2$	1
2	$Pd(CF_3CO_2)_2$	4
3	$PdCl_2$	28
4	$Pd(PPh_3)_2Cl_2$	23
5	$Pd(MeCN)_2Cl_2$	37
6	Na_2PdCl_4	37

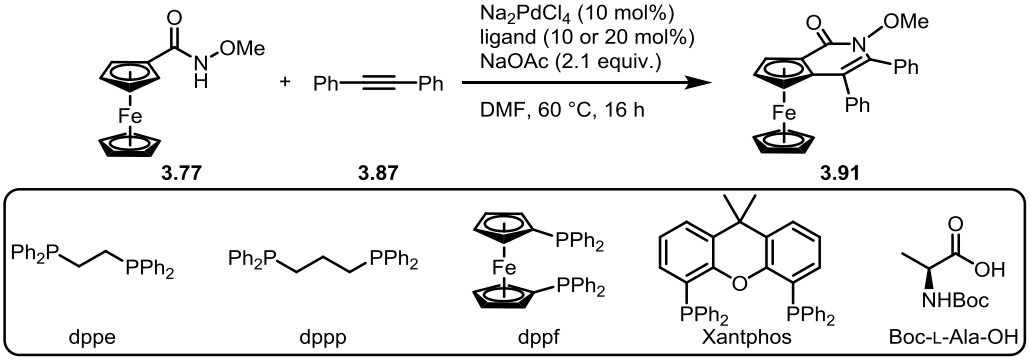
[a] yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard

Table 3.09. Screening of palladium sources

At this point, it was considered that the low yields observed could be as a result of the short catalyst lifetime, and a variety of ligands were screened in the hope of stabilising the catalyst (*Table 3.10*). All of the ligands screened suppressed the reaction to some extent and yields varied between 0 and 27%. Of the monodentate phosphorus ligands screened (*Table 3.10*, *entries 1-4*), P(2-furyl)$_3$ gave the optimum yield of 27%. The bidentate phosphorus ligands

screened reduced the yield of the reaction to a greater extent than the monodentate ones (*entries 5-9*). A 16% yield, the highest yield recorded with a bidentate phosphorus ligand, was observed with dppf and no reaction was observed with racemic BINAP.

The nitrogen-based ligands screened fared poorly and monodentate 2,6-dimethoxypyridine gave rise to a 17% yield whereas bidentate 2,2'-bipyridyl suppressed the reaction completely (*entries 10 and 11*). 2,6-Dimethoxypyridine was screened, as Yu had previously observed remarkable reactivity and selectivity when using the ligand in the arylation of sp^3 C–H bonds.[222] Amino acids as ligands have commonly been used in a variety of C–H functionalisations,[217-218] but protected amino acid Boc-L-Ala-OH only gave product **3.91** in 14% yield and as a racemic mixture (*entry 12*).



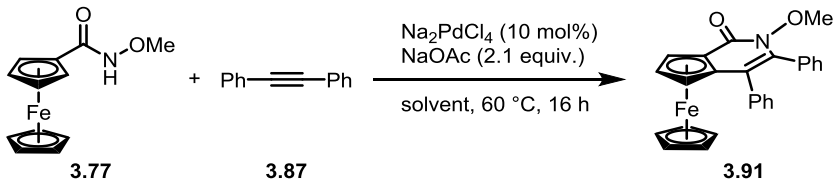
Entry	Ligand[a]	Yield (%)[a]
1	PPh_3	26
2	PCy_3	4
3	$P(o\text{-tol})_3$	17
4	$P(2\text{-furyl})_3$	27
5	dppe	3
6	dppp	9
7	dppf	16
8	Xantphos	13
9	(±)-BINAP	no reaction
10	2,6-dimethoxypyridine	17
11	2,2'-bipyridyl	no reaction
12	Boc-L-Ala-OH	14 (0% *ee*)

[a] monodentate ligands (20 mol%); bidentate ligands (10 mol%)
[b] yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard

Table 3.10. Screening of palladium sources

Finally, solvents for the reaction were screened but no improvement in yield was found

(*Table 3.11*). DMA was the only solvent, other than the structurally similar DMF, to facilitate product formation and the 26% yield obtained with DMA was still lower than the 37% obtained with DMF.



3.77 **3.87** **3.91**

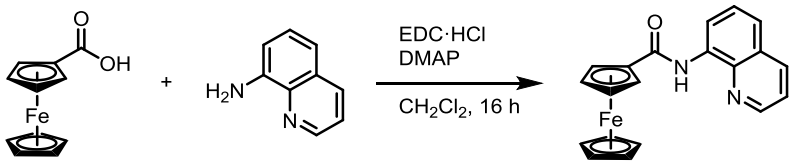
Entry	Solvent	Yield (%)[a]
1	DMA	26
2	DMF	37
3	Nitromethane	trace
4	MeCN	trace
5	DMSO	trace

[a] yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard

Table 3.11. Solvent screening

3.2.5 Investigating Alternative Ferrocene Substrates

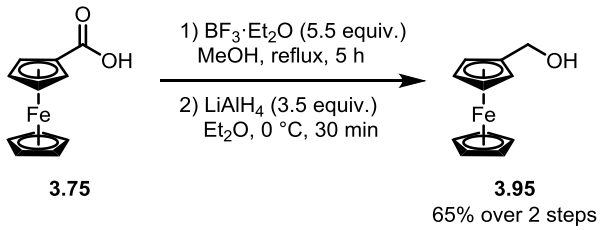
Since screening of the reaction parameters had led to no appreciable increase in yield, attention turned to the substrate, and more specifically the directing group. Quinoline amide **3.94** was synthesised in 59% yield directly from the parent carboxylic acid **3.75** using EDC coupling conditions (*Scheme 3.36*). 8-Amino quinoline has been recognised as a powerful directing group in recent years as it is able to bind the metal catalyst in a bidentate fashion.[223]



3.75 **3.93** **3.94**
59%

Scheme 3.36. Synthesis of quinoline amide **3.94**

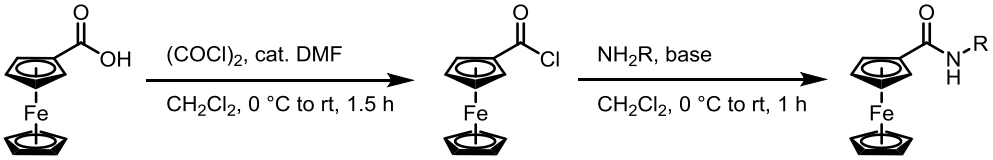
Alcohol **3.95**, a substrate containing a weak directing group (see *Scheme 3.05*), was synthesised in 65% yield over two steps from the parent carboxylic acid **3.75** (*Scheme 3.37*), with the intermediate ester used crude in the subsequent reduction step.



3.75 **3.95**
65% over 2 steps

Scheme 3.37. Reduction of carboxylic acid **3.75** to alcohol **3.95**

Some substrates were accessed using a divergent route involving common intermediate acid chloride **3.76**, which could be isolated with minimal purification and kept in the freezer without noticeable degradation for up to one month (*Table 3.12*). Acid chloride **3.76** was condensed with a variety of amines to give oxidative annulation substrates **3.96-3.98** in moderate to good yield.



3.75 **3.76** **3.96-3.98**

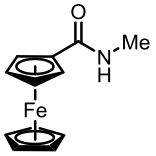
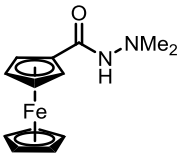
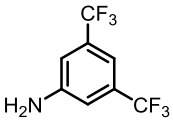
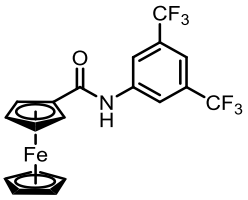
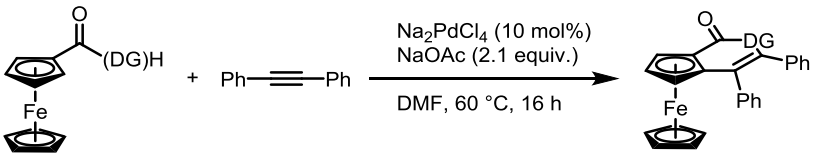
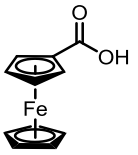
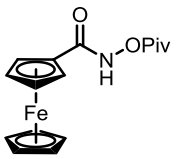
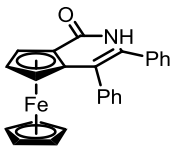
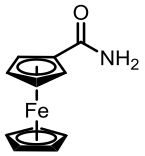
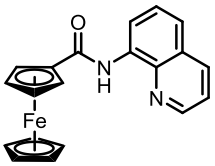
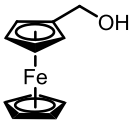
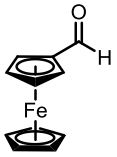
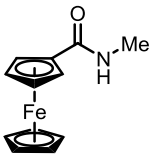
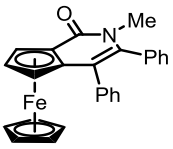
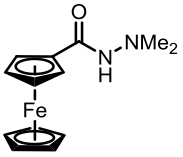
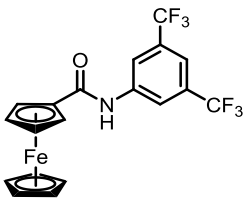
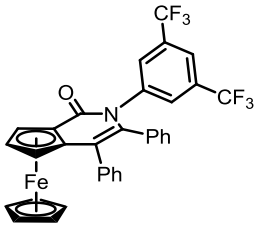
Entry	Amine	Base	Product	Yield (%)
1	$NH_2Me{\cdot}HCl$	NEt_3	 **3.96**	68
2	NH_2NMe_2	*N*-methylmorpholine	 **3.97**	74
3		NEt_3	 **3.98**	30

Table 3.12. Synthesis of substrates **3.96**-**3.98**

The prepared substrates were then subjected to the oxidative annulation conditions which had given annulation product **3.91** in 20% isolated yield (*Table 3.13*).



3.71 **3.87** **3.99**

Entry	Substrate	Yield[a]
1	 **3.75**	No reaction
2	 **3.78**	 9% **3.92** +  **3.89**
3	 **3.94**	No reaction
4	 **3.95**	 **3.100**
5	 **3.96**	 10% **3.101**
6	 **3.97**	No reaction
7	 **3.98**	 27% **3.102**

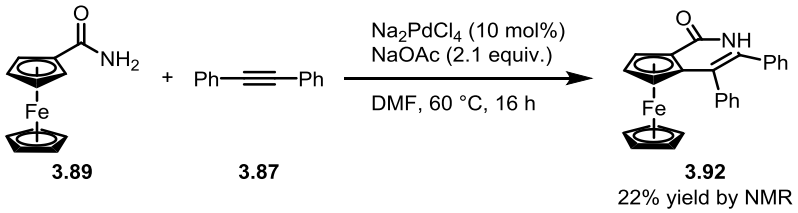
[a] yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard

Table 3.13. Oxidative annulation of alternative ferrocene substrates

Carboxylic acid **3.75**, which contains a weak directing group, did not undergo oxidative

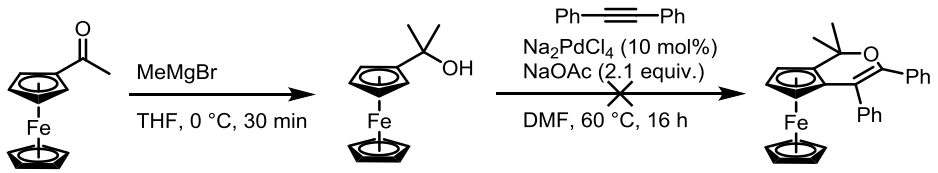
annulation but *N*-pivaloxycarboxamide **3.78** did, albeit with concomitant cleavage of the N–O bond and in only 9% NMR yield (*Table 3.13, entries 1 and 2*). Upon purification, it was discovered that the starting material had also undergone N–O bond cleavage, which demonstrated that pivaloxy is much more labile than a methoxy group. Substrate **3.94**, with the promising quinoline directing group, was found to be a poor substrate and no reaction occurred (*entry 3*). Alcohol **3.95** was rapidly consumed in the reaction but upon inspection of the ^{1}H NMR spectrum, alcohol **3.95** was found to have been oxidised to aldehyde **3.100**, evidenced by the singlet at 9.97 ppm (*entry 4*). *N*-Methylamide **3.96** underwent oxidative annulation to give product **3.101** in 10% yield (*entry 5*). Hydrazide **3.97** was synthesised in the hope that the N–N bond would be less labile than the N–O bond, but no reaction occurred with this substrate (*entry 4*). Finally, *N*-arylcarboxamide **3.98** was subjected to the reaction conditions and a relatively good 27% yield of product **3.102** resulted (*entry 7*).

Based on the above results a range of targeted substrates were synthesised, which would hopefully result in the exclusive formation of annulation product in high yield. Free amine **3.89** was isolated from the reaction of *N*-pivaloxycarboxamide **3.78** and subjected to the annulation conditions (*Scheme 3.38*). Although the reaction was successful, the product (**3.92**) was only formed in a disappointing 22% yield by ^{1}H NMR spectroscopy.



Scheme 3.38. Oxidative annulation of free amide **3.89**

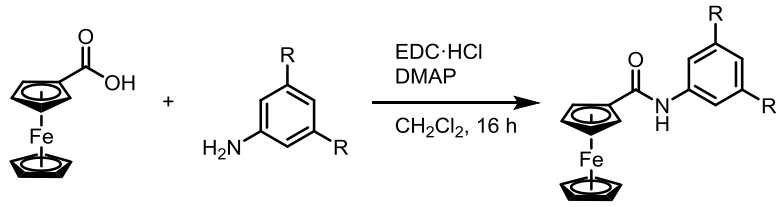
Since alcohol **3.98** was preferentially oxidised in the reaction, tertiary alcohol **3.104** (which is unable to undergo oxidation by virtue of the lack of α-hydroxy protons) was synthesised from ferrocene ketone **3.103** (*Scheme 3.39*). However, alcohol **3.104** proved unreactive and no reaction occurred.



3.103 **3.104** 55% **3.105**

Scheme 3.39. Synthesis and unsuccessful oxidative annulation of alcohol **3.104**

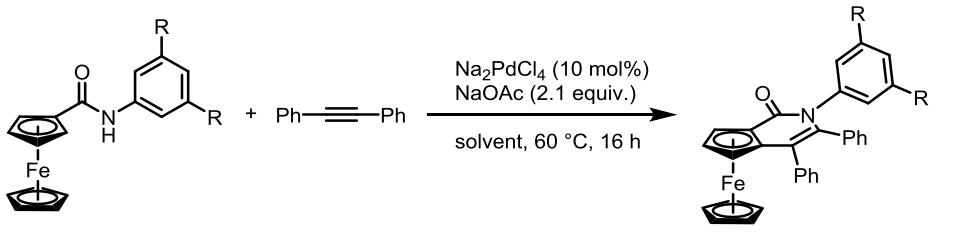
Given that the most promising result obtained when screening the alternative ferrocene substrates was the oxidative annulation of *N*-arylcarboxamide **3.98** in 27% yield, it was decided to synthesise a range of electronically different *N*-arylcarboxamides, in the hope of finding a directing group with the optimum electronic properties for a high-yielding oxidative annulation. *N*-Phenylcarboxamide **3.106** and *N*-3,5-dimethylphenylcarboxamide **3.107** were both accessed from the parent carboxylic acid **3.75** using EDC coupling conditions in 53% yield (*Scheme 3.40*).



3.75 R = H, Me **3.106**, R = H, 53% **3.107**, R = Me, 53%

Scheme 3.40. Synthesis of *N*-arylcarboxamides **3.106** and **3.107**

With these in hand, substrates **3.106** and **3.107** were subjected to the oxidative annulation conditions (*Scheme 3.41*); *N*-phenylcarboxamide **3.106** underwent annulation in 21% yield by ^{1}H NMR spectroscopy and *N*-3,5-dimethylphenylcarboxamide **3.107** in 13% yield.



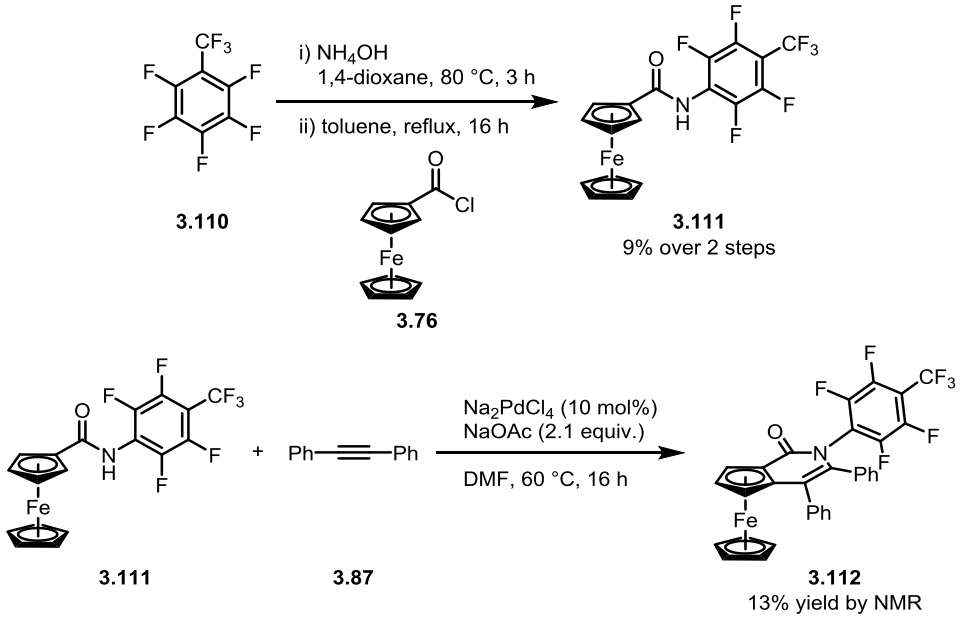
3.106, R = H
3.107, R = Me
3.87
3.108, R = H, 21% yield by NMR
3.109, R = Me, 13% yield by NMR

Scheme 3.41. Oxidative annulation of *N*-arylcarboxamides **3.106** and **3.107**

Comparing these results to the 27% yield obtained for the *N*-3,5-ditrifluoromethylphenylcarboxamide **3.98**, it appeared that the carboxamide with the

most electron-withdrawing aryl group gave the highest annulation yield. With this in mind, substrate **3.111**, with an extremely electron-withdrawing aryl group, was synthesised (*Scheme 3.42*). Octafluorotoluene **3.110** was first heated with ammonium hydroxide solution in a nucleophilic substitution reaction, which was then heated at reflux with acid chloride **3.76** to yield substrate **3.111**, albeit in a poor 9% yield over two steps.

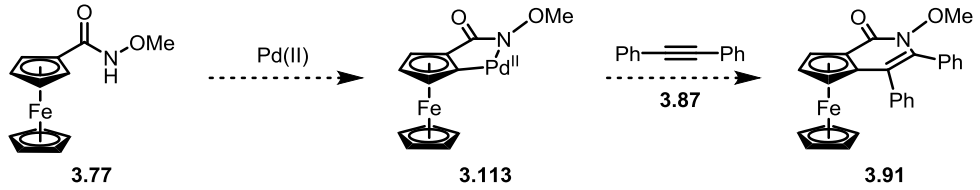
However, with substrate **3.111**, it was disappointing to observe annulation product **3.112** in only 13% yield—the same yield as was observed with *N*-3,5-dimethylphenylamide **3.107**. Therefore, it seemed that the trend previously observed (the more electron-withdrawing the *N*-aryl group, the higher the yield of oxidative annulation), did not hold true in this case.



Scheme 3.42. Synthesis and oxidative annulation of *N*-perfluorinatedarylcarboxamide **3.111**

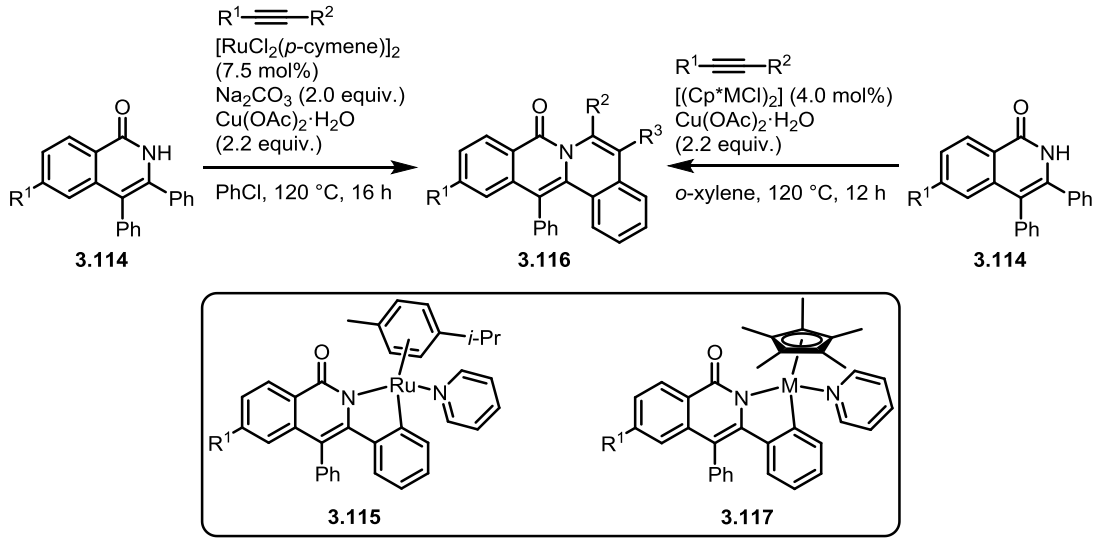
3.2.6 Preliminary Mechanistic Studies

At this stage, although a wide range of reaction conditions and substrates had been explored, no significant progress had been made. In order to continue, a better understanding of the reaction mechanism was sought, which would hopefully facilitate the optimisation of the reaction. To this end, the proposed palladacycle intermediate **3.113** was targeted (*Scheme 3.43*). Formation of palladacycle **3.113** and subsequent reaction with diphenylacetylene **3.87** might allow the identification of the problematic step of the reaction.



Scheme 3.43. Proposed synthesis of palladacycle **3.113**

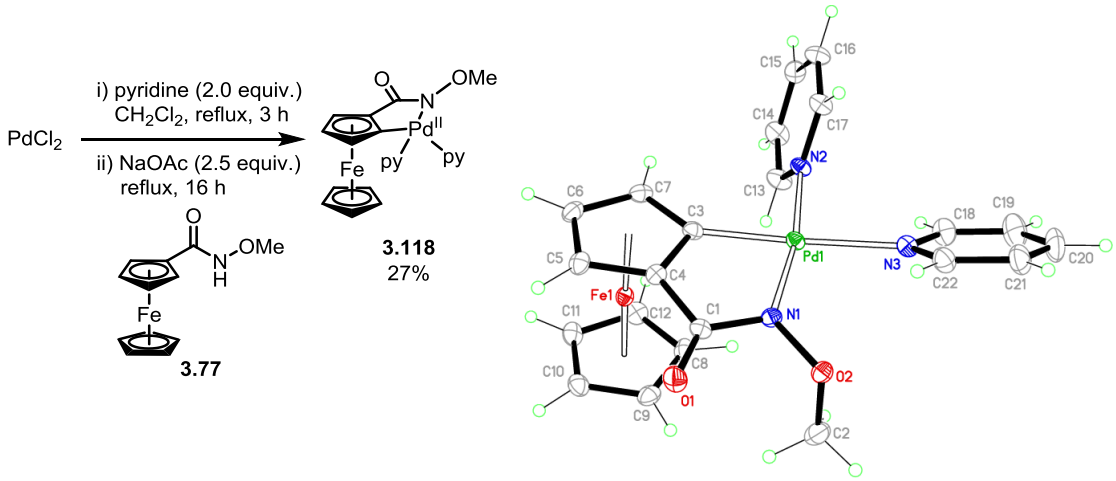
Wang recently conducted some thorough mechanistic studies into the Ru(II)-, Rh(III)- and Ir(III)-catalysed oxidative annulation of isoquinolones **3.114** with alkynes in which intermediates of the type **3.115** and **3.117** were isolated (*Scheme 3.44*).[148, 224] Both structures have pyridine ligands in addition to *p*-cymene and Cp* (the direct reaction of an isoquinolone substrate with stoichiometric metal catalyst did not result in any isolable product and the authors attributed this to an unstable 16 electron complex). It is only when the metal catalyst is first mixed with pyridine to form a catalyst of the type $[RuCl_2py(p\text{-cymene})]$ (py = pyridine) and reacted with isoquinolone **3.114**, that a stable plausible reaction intermediate could be isolated and the structure confirmed by single crystal X-ray crystallography.



Scheme 3.44. Oxidative annulation of isoquinolones **3.114** with alkynes

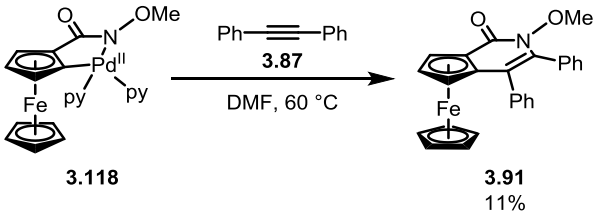
Inspired by this work, palladacycle **3.118**, which contained stabilising pyridine ligands to aid isolation, was sought (*Scheme 3.45*). Heating $PdCl_2$ with pyridine at reflux followed by heating with sodium acetate and *N*-methoxycarboxamide **3.77** pleasingly gave palladacycle **3.118** in 27% isolated yield. A single crystal X-ray structure was obtained of **3.118**,

confirming the structure and presence of two pyridine ligands. Interestingly, the two cyclopentadienyl rings of palladacycle **3.118** are eclipsed, unlike in oxidative annulation product **3.91** where they are staggered (see *Scheme 3.34*).



Scheme 3.45. Successful isolation and X-ray crystal structure of palladacycle **3.118**

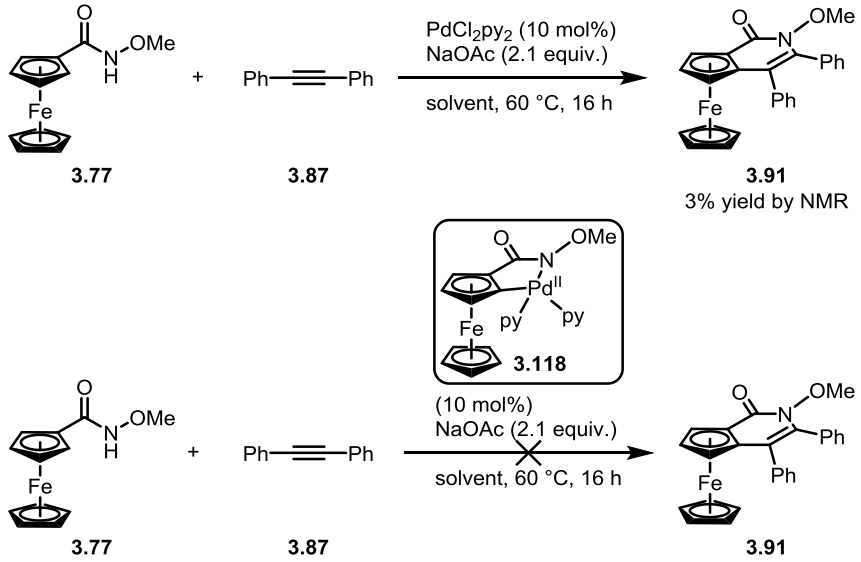
Whilst palladacycle **3.118** is not strictly a species in the reaction owing to the presence of two pyridine ligands, it nevertheless supports the initial C–H activation step in the mechanism. With this in mind, a 27% isolated yield for the formation of palladacycle **3.118** was disappointing and suggested that the first step in the reaction could be the problematic one. In order to evaluate the insertion of the alkyne into palladacycle intermediate **3.118**, palladacycle **3.118** was heated with diphenylacetylene **3.87** (*Scheme 3.46*). Although oxidative annulation product **3.91** was formed, it was only isolated in 11% yield alongside recovered starting material. This was again a low yield, suggesting that the alkyne insertion step could also be problematic.



Scheme 3.46. Reaction of palladacycle **3.118** with diphenylacetylene **3.87**

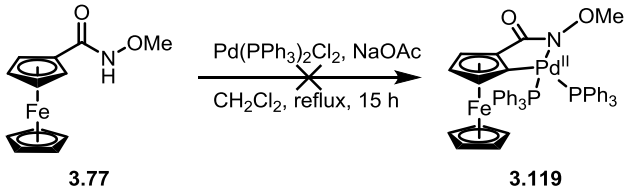
At this stage, owing to the poor yields obtained for both steps of the reaction, $PdCl_2py_2$ (the intermediate in the palladacycle synthesis) and palladacycle **3.118** itself were tested to

see whether either could catalyse the oxidative annulation (*Scheme 3.47*). Unfortunately, only a 3% yield by ^{1}H NMR spectroscopy was observed with $PdCl_2py_2$ and no reaction was observed with palladacycle **3.118**. This suggested that both catalysts were not viable for the reaction, probably due to the stability conferred to the complexes by the pyridine ligands.



Scheme 3.47. Screening $PdCl_2py_2$ and palladacycle **3.118** as catalysts

Replacing the pyridine ligands with triphenylphosphine ligands might increase the reactivity of the palladacycle and it had already been shown that the oxidative annulation reaction with $Pd(PPh_3)_2Cl_2$ was relatively successful (23% NMR yield, see *Table 3.09*). Therefore, compared to pyridine ligands, triphenylphosphine ligands are not detrimental to the reaction and allow the palladium catalyst to turnover. Once this was established, the triphenylphosphine analogue of palladacycle **3.118** (**3.119**) was targeted (*Scheme 3.48*). Unfortunately, this reaction proved unsuccessful and the ^{1}H NMR spectrum of the crude reaction was a complex mixture of products.



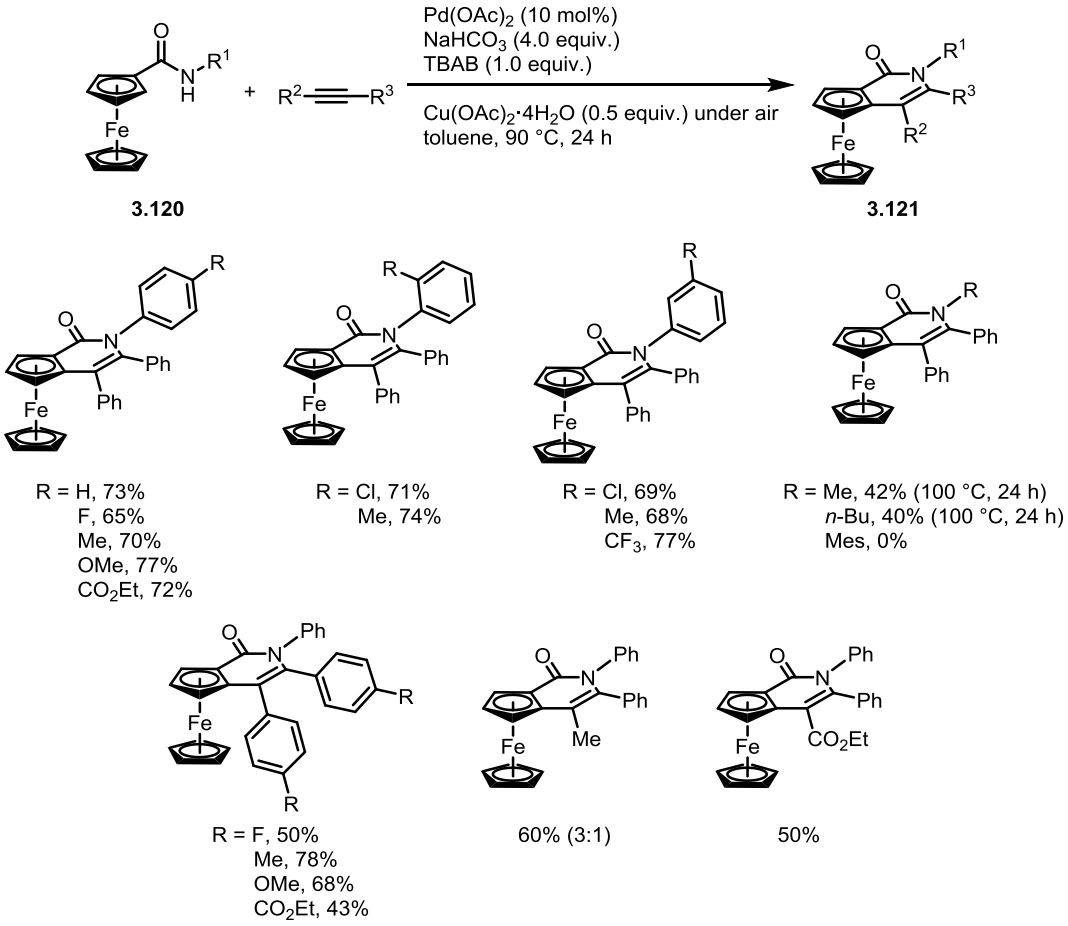
Scheme 3.48. Unsuccessful synthesis of palladacycle **3.119**

In conclusion, we were unable to optimise the oxidative annulation reaction and to identify

the problematic step. Our brief mechanistic investigations suggested that more than one step of the reaction might be problematic.

3.2.7 Successful Report of Oxidative Annulation of Ferrocenecarboxamides

Following this work, the high-yielding oxidative annulation of ferrocenecarboxamides **3.120** with alkynes was very recently reported using palladium catalysis (*Scheme 3.49*).[225] A range of electronically different *N*-arylcarboxamides underwent successful reaction with just two examples of *N*-alkylcarboxamides. The reaction showed good scope with a variety of diarylalkynes; alkylarylalkyne 1-phenyl-1-propyne **3.22** was also compatible, with the corresponding product isolated in 60% yield, albeit as a 3:1 mixture of regioisomers.



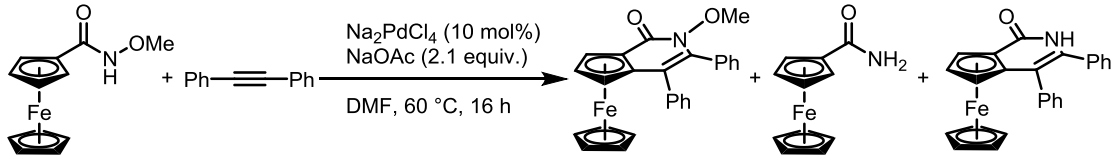
Scheme 3.49. Successful oxidative annulation of ferrocenecarboxamides **3.120**

Interestingly, during the optimisation of the reaction, DMF as a solvent proved ineffective and only a trace of product was observed. Furthermore, TBAB and $Cu(OAc)_2 \cdot 4H_2O$ were essential for reactivity, even though both reagents had failed to improve the yield of the

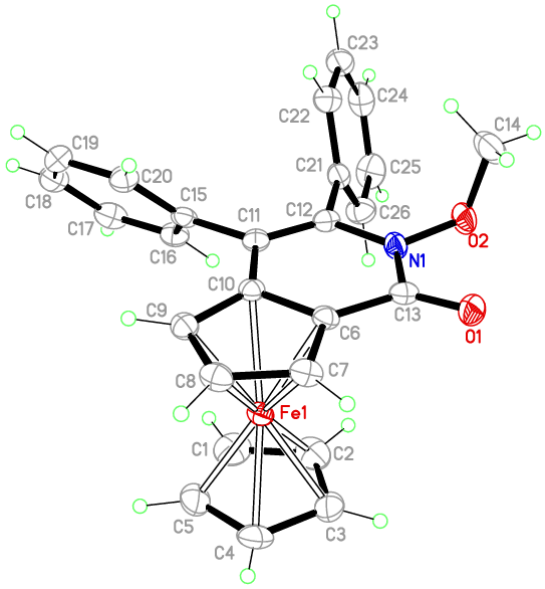
oxidative annulation of *N*-methoxyferrocenecarboxamide **3.77** in our hands, as detailed above.

3.3 Conclusions

In conclusion, the oxidative annulation of *N*-methoxyferrocenecarboxamide **3.77** and a variety of derivatives with diaryl- and alkylarylalkynes was successfully achieved (*Scheme 3.50*). With *N*-methoxycarboxamide **3.77** and diphenylacetylene **3.77**, 20% annulation product **3.91** was isolated, alongside 4% of analogous product **3.92**, in which the N–O had cleaved.



3.77 **3.87** **3.91** 20% **3.89** 20% **3.92** 4%



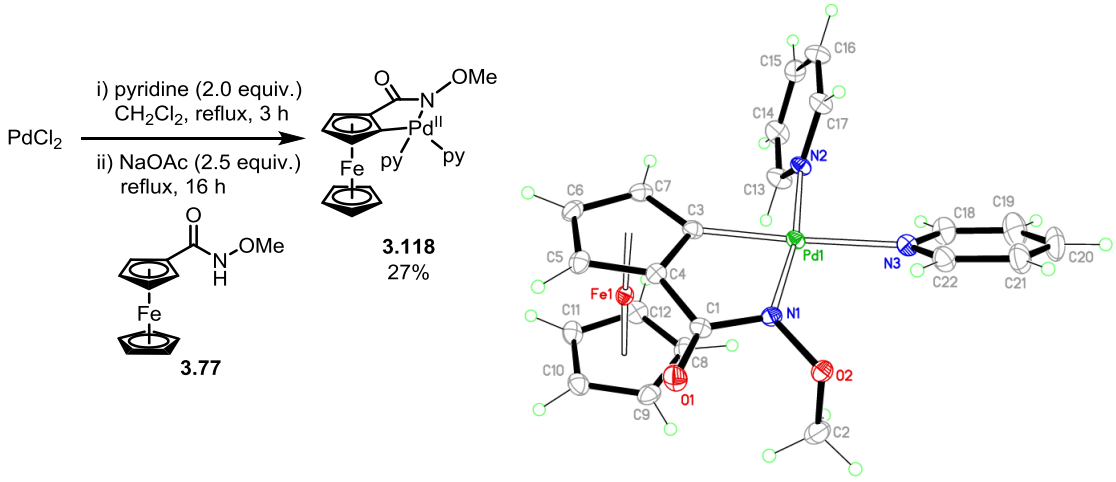
3.91

Scheme 3.50. Successful oxidative annulation of *N*-methoxyferrocenecarboxamide **3.91**

Although a wide range of reaction parameters were screened, the reaction proved difficult to optimise and no significant increase in the yield of the reaction above 30% could be made. However, potential reaction intermediate palladacycle **3.118** was synthesised, isolated and the structure of **3.118** confirmed through X-ray crystallographic analysis (*Scheme 3.51*). Unfortunately, reactions to further utilise palladacycle **3.118**, which it was hoped would help

identify the problematic step of the reaction, were unsuccessful.

The recent report of the successful high-yielding oxidative annulation of ferrocenecarboxamides,[225] demonstrated that the reaction could be optimised through the careful selection and combination of reagents. The challenge now remains to render the oxidative annulation enantioselective.



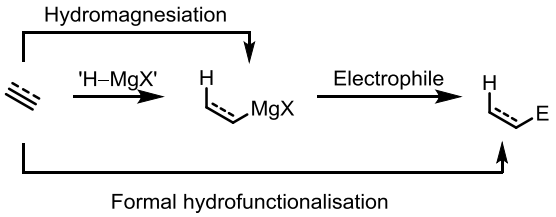
Scheme 3.51. Successful isolation and X-ray crystal structure of palladacycle **3.118**

Following the investigation of two palladium-catalysed reactions, the focus of research changed and iron catalysis was explored, in the hope of developing some more sustainable and environmentally benign methodology. Building on previous work in the Thomas group,[226] the iron-catalysed hydrofunctionalisation of olefins was pursued.

Chapter 4. Hydromagnesiation for the Hydrofunctionalisation of Alkenes

4.1 Introduction

The formal addition of 'H–MgX' across an alkene or alkyne is known as hydromagnesiation[227] (*Scheme 4.01*) and provides a simple method for the formation of Grignard reagents.[228-229] Where Grignard reagents are difficult to synthesise *via* the conventional insertion of magnesium metal into a carbon–halogen bond, hydromagnesiation is an alternative. Upon reaction of the prepared Grignard reagent with an electrophile, a formal hydrofunctionalisation reaction of the olefin has occurred.[230]



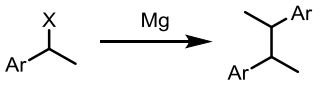
Scheme 4.01. Hydromagnesiation and formal hydrofunctionalisation of olefins

4.1.1 Using MgH_2

MgH_2 itself can be used for hydromagnesiation, although the uncatalysed reaction is poor yielding and requires forcing reaction conditions.[231] In 1978 Ashby and Smith showed that using MgH_2 with Cp_2TiCl_2 as a catalyst, hydromagnesiation occurs under much milder conditions and the product obtained after quenching the Grignard reagent with an electrophile can be isolated in high yield (*Table 4.01*).[232]

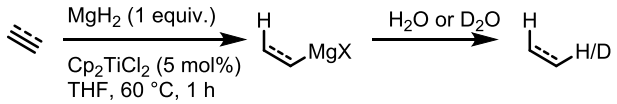
A range of olefins underwent successful hydromagnesiation and with the exception of styrene (*Table 4.01*, *entry 2*), all olefins generated terminal Grignard reagents. The major regioisomeric product for the reaction with styrene, however, was the internal benzylic Grignard reagent (9:1 internal:terminal), presumably as a result of the stabilisation conferred to the organometallic intermediate by the aromatic ring. Compared to the other substrates, styrene was also more reactive—100% product was obtained in only one hour at room temperature. Benzylic Grignard reagents can be challenging to synthesise by conventional

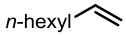
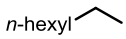
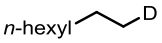
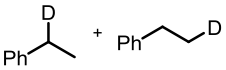
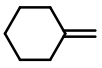
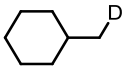
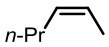
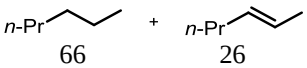
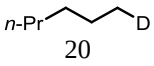
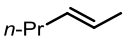
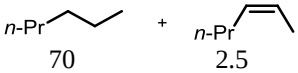
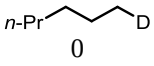
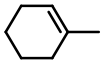
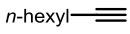
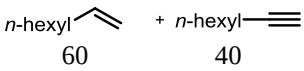
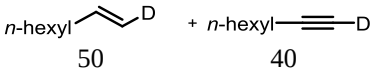
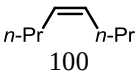
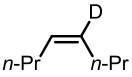
reductive insertion owing to competing Wurtz homocoupling (*Scheme 4.02*),[233-234] so hydromagnesiation offers an alternative and highly efficient route.



Scheme 4.02. Wurtz homocoupling as a byproduct of Grignard reagent formation

In addition to monosubstituted alkenes, 1,1- and 1,2-disubstituted alkenes also underwent hydromagnesiation (*entries 3-5*), although the yields were poorer with the latter and some double bond isomerisation was observed. No reaction occurred when a trisubstituted alkene was tested (*entry 6*).



Entry	Substrate	Reaction time (h)	Product (%)	
			With H_2O	With D_2O[a]
1		1	 98	 93
2		1 (rt)	 100	 90 10
3		48	 95	 60
4		68	 66 26	 20
5		92	 70 2.5	 0
6		no reaction	-	-
7		1 (rt)	 60 40	 50 40
8		1 (rt)	 100	 65

[a] remaining material protonated product

Table 4.01. Titanium-catalysed hydromagnesiation of olefins

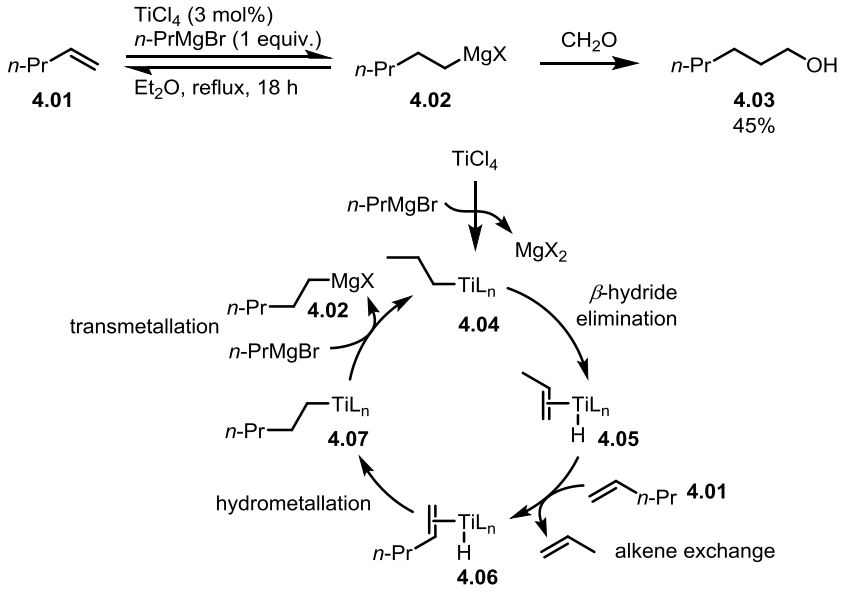
The substrate scope was successfully extended to alkynes and the products were consistent with *syn* addition of 'H–MgX' (*entries 7 and 8*). Competitive deprotonation occurred when 1-octyne was subjected to hydromagnesiation, whilst 4-octyne underwent hydromagnesiation efficiently. For the more sterically hindered olefins, the yield of the deuterated product was

significantly lower than for the corresponding protonated product, with increasing amounts of the protonated product observed. The low yields were attributed to the relatively long reaction times required for the conversion of sterically hindered olefins, during which time the active magnesium species decomposes.

Bogdanović and co-workers have subsequently reported the hydromagnesiation of alkyl alkenes using MgH_2 with titanium, zirconium, hafnium and chromium catalysts.[235-236]

4.1.2 Using *β*-hydrogen Containing Grignard Reagents

Alternatively, hydromagnesiation can be achieved using *β*-hydrogen containing Grignard reagents in the presence of a transition-metal. In the 1960s Cooper and Finkbeiner observed a Grignard exchange reaction between a monosubstituted alkene and a Grignard reagent in the presence of titanium tetrachloride.[237-238] For example, the titanium-catalysed reaction of 1-pentene **4.01** with *n*-propylmagnesium bromide, followed by subsequent trapping with formaldehyde, led to 1-hexanol **4.03** in 45% yield (*Scheme 4.03*).



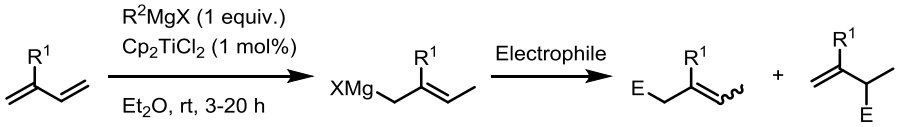
Scheme 4.03. Grignard exchange reaction between 1-pentene **4.01** and *n*-propylmagnesium bromide

The proposed mechanism begins with the alkylation of titanium tetrachloride to give alkyltitanium species **4.04**. *β*-Hydride elimination then gives the active titanium hydride species **4.05**; following alkene exchange, hydrometallation gives organotitanium **4.07**, which then undergoes transmetallation with *n*-propylmagnesium bromide to give Grignard reagent

4.02.

Cooper and Finkbeiner went on to extend the $TiCl_4$-catalysed hydromagnesiation to a number of alkenes, including styrene,[239] and electrophiles, including aldehydes, ketones, carbon dioxide, orthoesters and oxygen. With the exception of styrene, terminal Grignard reagents were generally the sole regioisomeric product. Cp_2TiCl_2, $Ti(O\text{-}i\text{-}Pr)_4$, $ZrCl_4$ and VCl_4 were also found to be effective hydromagnesiation catalysts. In comparison, $FeCl_3$ was a poor catalyst for the hydromagnesiation of styrene, with only a 15% yield of phenylethyl alcohols determined following oxidation of the Grignard intermediate.

Titanium-catalysed hydromagnesiation has also been extended to dienes and internal alkynes, giving allyl (**4.09**) and 1,2-*cis*-disubstituted vinyl (**4.13** and **4.14**) Grignard reagents, respectively (*Tables 4.02 and 4.03*).[240-241] Following reaction with an electrophile (water, aldehydes, ketones, carbon dioxide, nitriles, iodine and organohalides), the product was generally obtained in high yield.[229] The higher yields for dienes and disubstituted alkynes compared to monosubstituted alkenes (with the exception of styrene) was attributed to the greater stability of allyl and vinyl Grignard reagents compared to alkyl Grignard reagents, which renders the hydromagnesiation irreversible.[240]



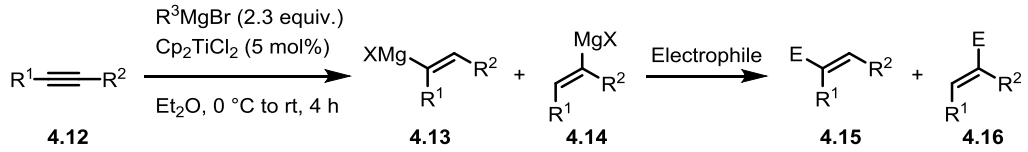
4.08 **4.09** **4.10** **4.11**

Entry	R^1	R^2MgX	Electrophile	E	Products (%)
1	H	*n*-PrMgBr	H_2O	H	*trans*-**4.10**, 13 *cis*-**4.10**, 13 **4.11**, 53
2	H	*n*-PrMgBr	Me_2CO	$Me_2C(OH)$-	**4.11**, 79
3	Me	*n*-PrMgBr	H_2O	H	**4.10**, 21 **4.11**, 76
4	Me	*n*-PrMgBr	Me_2CO	$Me_2C(OH)$-	**4.11**, 95

Table 4.02. Hydromagnesiation of 1,3-dienes

For isoprene (R^1 = Me), the hydromagnesiation was selective for allyl Grignard reagent **4.09** and trapping with an electrophile gave terminal alkene **4.11** as the major product (*Table 4.02, entries 3 and 4*).

The hydromagnesiation of disubstituted alkynes proceeded with *syn* addition (*Table 4.03*) and with low regioselectivity for unsymmetrical dialkylalkynes (*Table 4.03, entry 1*). When the alkyne substituent was a trimethylsilyl or hydroxymethyl group, the regioselectivity of the hydromagnesiation was controlled, with the vinyl Grignard reagent generated α to the trimethylsilyl group and β to the hydroxymethyl group (*entries 2 and 3*).



4.12 **4.13** **4.14** **4.15** **4.16**

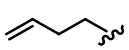
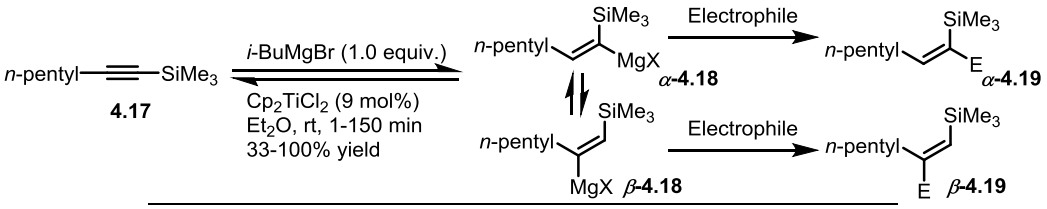
Entry	R^1	R^2	R^3MgX	Electrophile	E	Products (%)
1	*n*-Pr	Me	*i*-BuMgBr	I_2	I	**4.15**, 42 **4.16**, 58
2	*n*-pentyl	$SiMe_3$	*i*-BuMgBr	CuI		**4.16**, 86
3	*n*-Bu	CH_2OH	*i*-BuMgCl	I_2	I	**4.15**, 78-86

Table 4.03. Hydromagnesiation of disubstituted alkynes

Interestingly, the regioselectivity of the hydrofunctionalisation of silylacetylene **4.17** was found to depend on the electrophile used (*Table 4.04*).[242] The reaction time for each electrophile varied owing to the different lengths of time necessary for the reaction to reach completion. The ratio of α-**4.19**:β-**4.19** varied between 77:23 and >99:1 and the observed difference in regioisomeric ratio was rationalised by the difference in the rate of the vinyl Grignard reagent α-**4.18** and β-**4.18** interconversion with the rates of reaction of the Grignard reagents with electrophile.



Entry	Electrophile	E	Products α-4.19:β-4.19
1	D_2O	D	77:23
2	Me_3SiOTf	$SiMe_3$	77:23
3	R_1R_2CO	$R_1R_2C(OH)$	81-94:19-6
4	CBr_4	Br	>99:<1

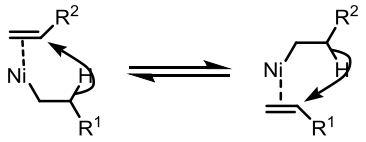
Table 4.04. Electrophile dependent regioselectivity

The majority of recent hydromagnesiation reports have focused on the transformation of alkylaryl- and silylarylacetylenes using titanium catalysis. These reactions were regio- and

stereoselective; both alkynes gave *cis*-*α*-aryl vinyl Grignard reagents. The prepared Grignard reagents were subsequently used in reactions with alkyl iodides,[243] carbonyls,[244] trialkylstannyl chlorides,[245-247] arylselenenyl bromides,[248] aryltellurenyl iodides,[249] and in cross-coupling reactions.[246, 250-251]

In addition to titanium, other transition-metals have also been used to catalyse hydromagnesiation, including zirconium,[235] nickel,[252-254] cobalt[255] and iron.[256-257]

Mechanistic investigations into nickel-catalysed hydromagnesiation suggested that the key step in the reaction involved *β*-hydride transfer from an alkyl group to a coordinated alkene within an organonickel complex (*Scheme 4.03*), as opposed to the formation of a distinct nickel-hydride species through *β*-hydride elimination.[252-254] Two observations were given in support of this hypothesis: firstly, formation of an active homogenous catalyst required an alkene, and secondly, the isomerisation of (2-phenylethyl)magnesium bromide to the more thermodynamically stable (1-phenylethyl)magnesium bromide was promoted by the addition of an alkene.



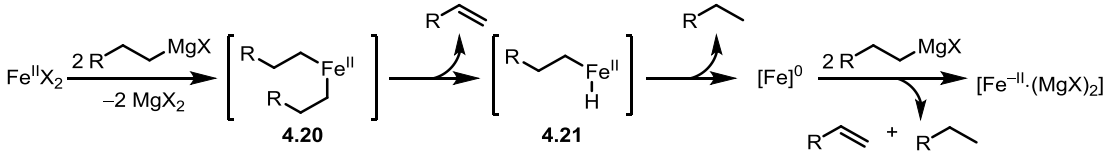
Scheme 4.03. *β*-Hydride transfer

4.1.2.1 Iron-Catalysed Hydromagnesiation

Following Tamura and Kochi's seminal report of the iron-catalysed hydromagnesiation of monsubstituted alkenes using $FeCl_3$,[256-257] a number of years passed before the area was revisited. In 2012 however, there were three separate reports of iron-catalysed hydromagnesiation[258] and each focused on the transformation of a different substrate, namely alkyl alkenes,[259] aryl alkenes[226] and alkynes.[260]

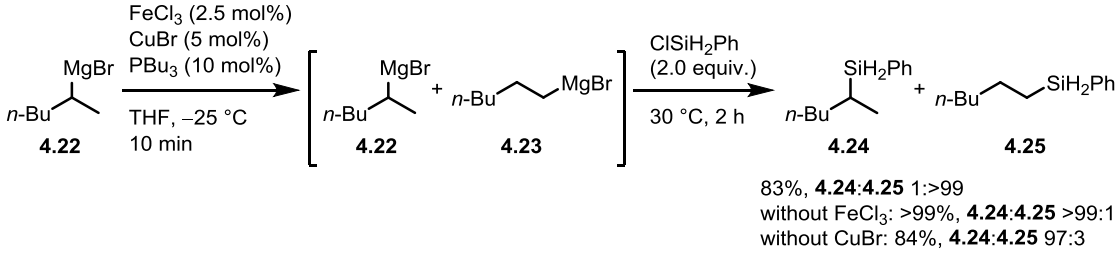
The action of *β*-hydrogen containing Grignard reagents on Fe(II) salts reduces the iron precatalyst to a low-valent highly active species.[34-35, 38, 261] This is considered to be the first step in the mechanism for all iron-catalysed hydromagnesiations using *β*-hydrogen containing Grignard reagents. Although there is no consensus as to the exact oxidation state

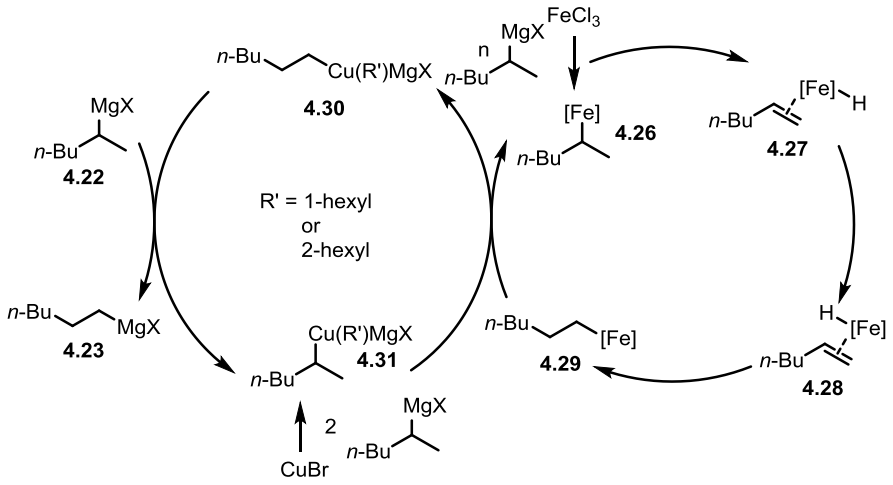
of the iron species, Bogdanović and co-workers proposed Fe(−II) (*Scheme 4.04*). Alkylation of FeX_2 by the Grignard reagent results in iron dialkyl species **4.20**. Following *β*-hydride elimination (**4.20**) and reductive elimination, Fe(0) is formally reached. Reduction with two more equivalents of Grignard reagent formally leads to Fe(−II) complex $[Fe^{-II}\cdot(MgX)_2]$.



Scheme 4.04. Generation of low-valent iron species

Shirakawa and Hayashi recently reported the isomerisation of secondary alkyl Grignard reagents to the thermodynamically more stable primary alkyl Grignard reagents using cooperative iron-copper catalysis (*Scheme 4.05*);[262] for example, 2-hexylmagnesium bromide **4.22** was smoothly converted into terminal silane **4.25** *via* 1-hexylmagnesium bromide **4.23** in 83% yield.

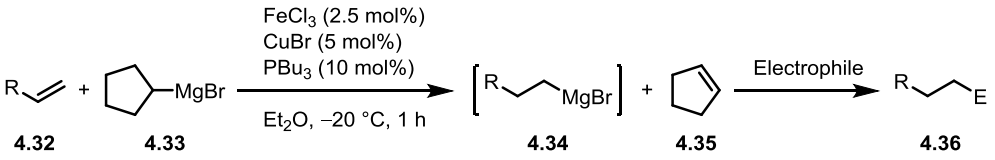




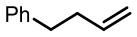
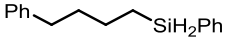
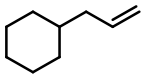
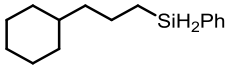
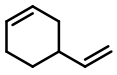
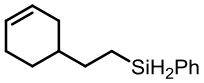
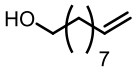
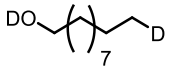
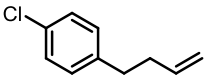
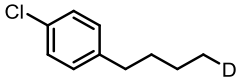
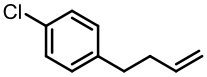
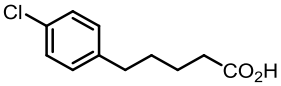
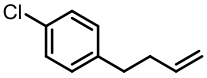
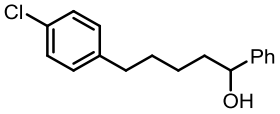
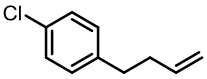
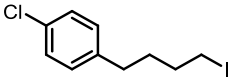
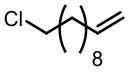
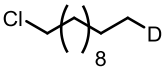
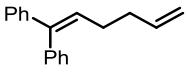
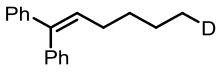
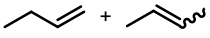
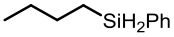
Scheme 4.05. Isomerisation of secondary to primary Grignard reagents

Isomerisation did not occur in the absence of $FeCl_3$ or CuBr and it was postulated that iron facilitated the isomerisation and copper, the transmetallation between iron and magnesium.

Building on this work, if a terminal alkene was added to the reaction then an alkene-Grignard exchange occurred (*Table 4.05*).[259] Significantly, when a secondary Grignard reagent such as cyclopentylmagnesium bromide **4.33** was used (the hydromagnesiation of the resultant cyclopentadiene **4.35** would be slow compared to the hydromagnesiation of a terminal alkene), the reaction was rendered irreversible and thereby driven to completion. A range of terminal alkenes and electrophiles were investigated.



4.32 **4.33** **4.34** **4.35** **4.36**

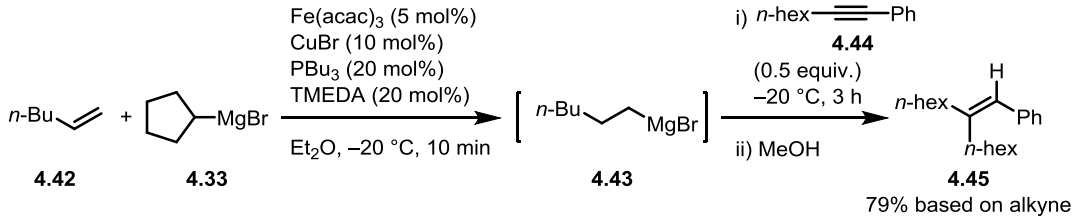
Entry	Substrate	Electrophile	Product	Yield (%)
1		$ClSiH_2Ph$		72
2		$ClSiH_2Ph$		68
3		$ClSiH_2Ph$		51
4	 **4.37**	D_2O		80 (93%-*d*)
5	 **4.38**	D_2O		72 (96%-*d*)
6		CO_2		75
7		PhCHO		73
8		I_2		81
9[a]		D_2O		69 (96%-*d*)
10	 **4.39**	D_2O	 **4.40**	91 (94%-*d*)
11	 1:1	$ClSiH_2Ph$	 **4.41**	76

[a] $FeCl_3$ (2.5 mol%), $Ph_2P(CH_2)_3NMe_2$ (5 mol%), $[CuI(PBu_3)]_4$ (5 mol% Cu), Et_2O, −40 °C used

Table 4.05. Hydromagnesiation of terminal alkyl alkenes and selected examples

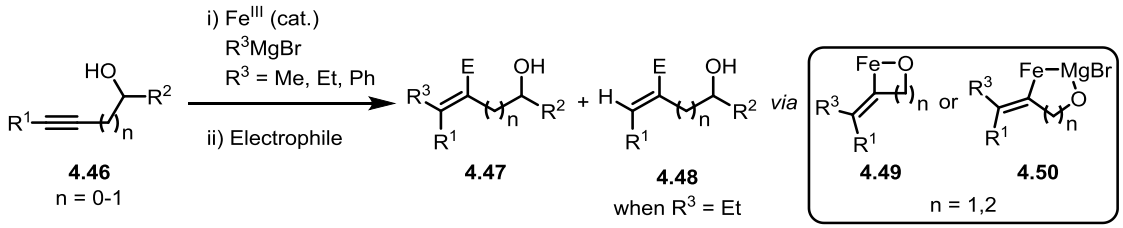
Notably, alcohol **4.37** and chloroarene **4.38** were compatible with the methodology, which is in contrast to what would be observed using the conventional insertion of magnesium metal

into a carbon–halogen bond (*Table 4.05, entries 4-8*) (the alkyl Grignard reagent from the reaction of chloroarene **4.38** would be difficult to prepare selectively from the corresponding dihalo compound). Alkene **4.40** was isolated as the exclusive product for **4.39**, whereas competitive radical cyclisation would occur when subjecting **4.39** to conventional Grignard formation conditions (*entry 10*). Silane **4.41** was also isolated as the sole regioisomer when a 1:1 mixture of 1-butene and (*E*)- and (*Z*)-2-butene underwent hydromagnesiation (*entry 11*). These primary Grignard reagents were subsequently used in an iron-catalysed carbomagnesiation protocol where Grignard reagent **4.43** was used in the carbomagnesiation of 1-phenyl-1-octyne **4.44** to give alkene **4.45** in high yield (*Scheme 4.06*).



Scheme 4.06. Tandem hydromagnesiation-carbomagnesiation protocol

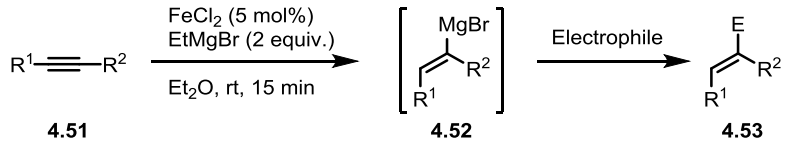
Interestingly, no hydromagnesiation was observed in the carbomagnesiation step even though a Grignard reagent bearing *β*-hydrogens was used. This is in contrast to that observed by Ready and co-workers in the iron-catalysed carbomagnesiation of propargylic and homopropargylic alcohols **4.46**—when using ethylmagnesium bromide, small amounts of product (**4.48**) arising from competitive hydromagnesiation were observed (*Scheme 4.07*).[263] However, the iron precatalyst in this case was an Fe(III) salt ($Fe(acac)_3$ (acac = acetylacetonate) or $Fe(ehx)_3$ (ehx = 2-ethylhexanoate)).



Scheme 4.07. Carbomagnesiation of propargylic and homopropargylic alcohols

The second recent report of iron-catalysed hydromagnesiation, by Nakamura and co-workers, focused on the selective *cis*-hydromagnesiation of alkynes **4.51** using $FeCl_2$ and

ethylmagnesium bromide (*Table 4.06*).[260] No competing carbomagnesiation was observed in this case.



4.51 **4.52** **4.53**

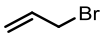
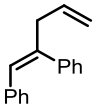
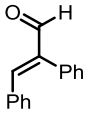
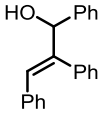
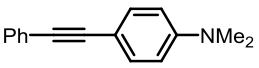
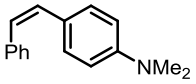
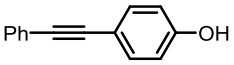
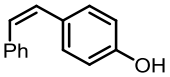
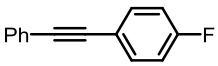
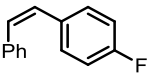
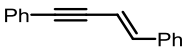
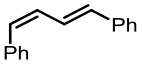
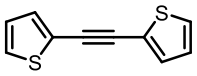
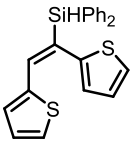
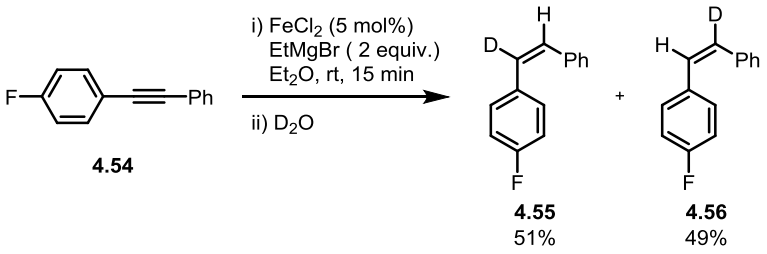
Entry	Alkyne	Electrophile	Product (%)	*E:Z*
1		HCl	 94	2:98
2			 72	3:97
3			 67	98:2
4		PhCHO	 73	>99:1
5		HCl	 73	14:86
6		HCl	 75	11:89
7		HCl	 81	6:94
8		HCl	 42	18:82
9		$ClSiHPh_2$	 38	>99:1

Table 4.06. *Cis*-hydromagnesiation of alkynes

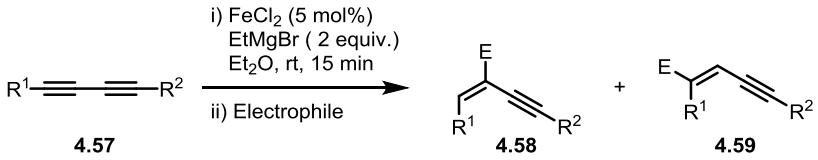
A range of diarylalkynes bearing both electron-donating and electron-withdrawing substituents were tolerated and the products were consistently generated in excellent stereoselectivity. However, the hydromagnesiation was not regioselective, as demonstrated through the hydromagnesiation and subsequent trapping of unsymmetrical alkynes—a

roughly 1:1 mixture of regioisomers **4.55** and **4.56** was obtained when the Grignard intermediate generated from alkyne **4.54** was quenched with D_2O (*Scheme 4.08*).



Scheme 4.08. Hydromagnesiation of unsymmetrical alkyne **4.55**

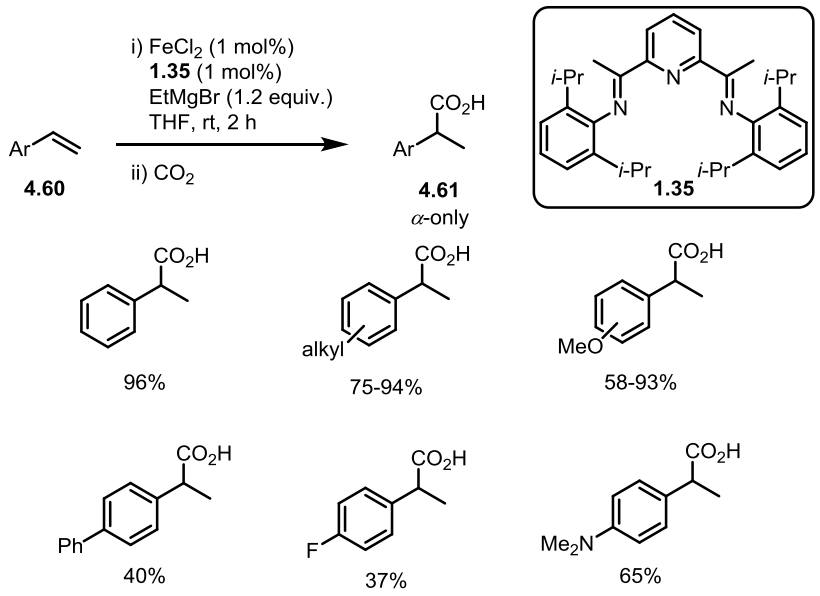
Notably, alkylalkynes and alkenes did not undergo hydromagnesiation when subjected to the reaction conditions, but this methodology was successfully extended to the monohydromagnesiation of 1,3-diynes **4.57** (*Table 4.07*). In this case, the hydromagnesiation was regioselective and the electrophile was added to the carbon α to the intact triple bond. For the unsymmetrical diyne 1-phenyl-4-trimethylsilylbutadiyne, hydromagnesiation was selective for the phenyl-substituted alkyne (*entry 5*). The mechanism of this particular reaction is unclear but the authors suggest that a radical mechanism may be operating, as opposed to a purely organometallic one.



Entry	Substrate	Electrophile	Yield (%)	*E*:*Z*	4.58:4.59
1	Ph—≡—≡—Ph	D_2O	63	14:86	>99:1
2	Ph—≡—≡—Ph	DMF	50	97:3	>99:1
3	F—Ph—≡—≡—Ph—F	D_2O	63	11:89	97:3
4	MeO—Ph—≡—≡—Ph—OMe	D_2O	65	22:78	97:3
5	Ph—≡—≡—$SiMe_3$	D_2O	55	17:83	98:2

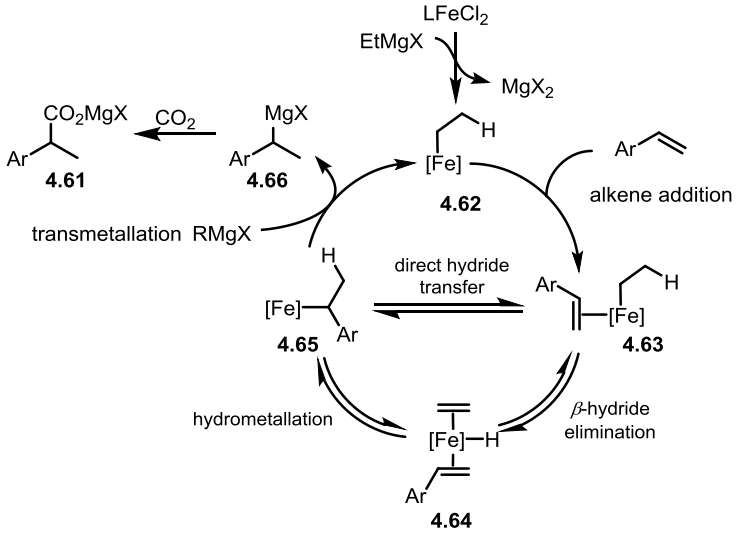
Table 4.07. Hydromagnesiation of 1,3-diynes

The hydrocarboxylation of styrene derivatives **4.60** using a highly regioselective hydromagnesiation was recently reported by Thomas and co-workers (*Scheme 4.09*).[226] Using $FeCl_2$ and bis(imino)pyridine ligand (BIP) **1.35** as a precatalyst, the reaction was found to be particularly well suited to substrates bearing electron-donating groups and substituents in all the positions of the aryl ring were tolerated.



Scheme 4.09. Hydrocarboxylation of styrene derivatives and selected examples

Mechanistic studies of the reaction suggested a mechanism similar to that proposed for the titanium-catalysed Grignard exchange reaction (see *Scheme 4.10*).



Scheme 4.10. Proposed hydrocarboxylation mechanism

Initial alkylation of $FeCl_2$ by ethylmagnesium bromide followed by styrene coordination gives rise to iron alkyl species **4.63**. Hydrometallation can now take place *via* two pathways and it has so far proven difficult to determine which pathway is operating. *β*-Hydride elimination leads to iron hydride species **4.64**, which can add across styrene to give iron alkyl species **4.65** as a single *α*-regioisomer. Alternatively, iron alkyl species **4.63** can transfer a hydride directly from the ethyl group to styrene to give iron alkyl **4.65**. Following

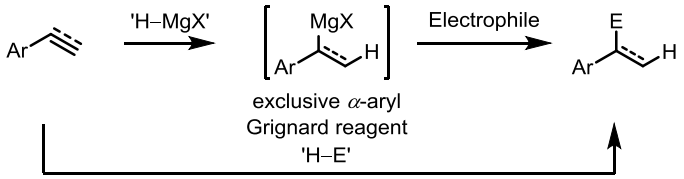
transmetallation from iron to magnesium, the resultant benzylic Grignard reagent **4.66** was trapped with carbon dioxide.

The three recent hydromagnesiation reports highlight the utility of this reaction for the preparation of Grignard reagents that would otherwise be difficult to synthesise. Iron-catalysed hydromagnesiation remains a relatively underexplored area and thus further research into the reaction scope and mechanism will hopefully result in the reaction becoming commonplace in synthetic sequences.

4.2 Results and Discussion

4.2.1 Aims

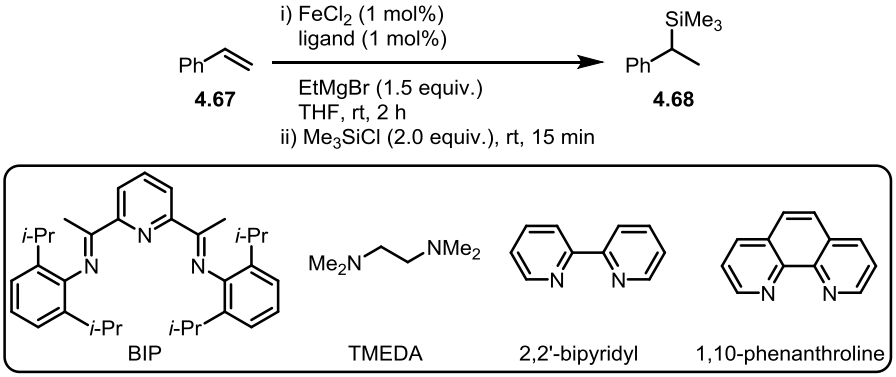
Building upon the iron-catalysed highly regioselective formal hydrocarboxylation of styrene derivatives,[226] we aimed to exploit the iron-catalysed hydromagnesiation procedure to explore the range of electrophiles that could be trapped (*Scheme 4.11*). In doing so, we aimed to develop a broad hydrofunctionalisation procedure that was operationally simple to perform and would be capable of forming a range of carbon–carbon and carbon–heteroatom bonds.



Scheme 4.11. Formal hydrofunctionalisation of olefins

4.2.2 Catalyst Simplification

As the hydrocarboxylation methodology relied on bis(imino)pyridine ligand (BIP) **1.35**, which is either expensive to buy or requires synthesis *via* a Schiff base condensation reaction from the corresponding 2,6-diacetylpyridine and aniline,[70] other ligands for the hydromagnesiation were explored. Using styrene **4.67** as a model substrate and trimethylsilyl chloride as a model electrophile, *N*,*N*,*N*',*N*'-tetramethylethylenediamine (TMEDA), 2,2'-bipyridyl and 1,10-phenanthroline were tested (*Table 4.08*). As controls, the reaction was also conducted in the absence of ligand and with BIP.



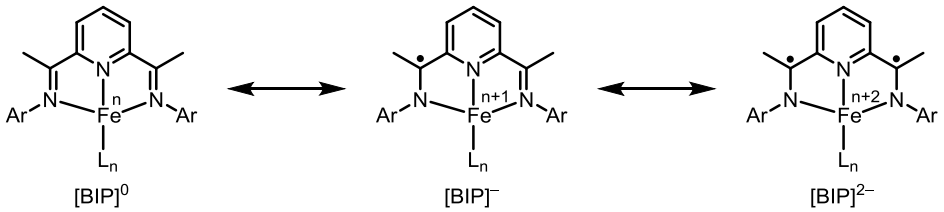
Entry	Ligand	Yield 4.68 (%)[a]
1	-	42 (50% **4.67**)
2	BIP	84
3	TMEDA	92
4	2,2'-bipyridyl	75
5	1,10-phenanthroline	73

[a] yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard

Table 4.08. Ligand optimisation

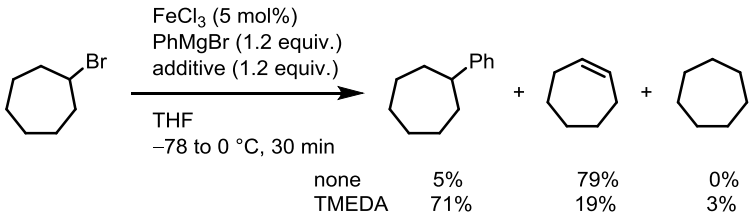
In the absence of ligand, silane **4.68** was observed in 42% yield and 50% styrene **4.67** was recovered, highlighting the necessity for a ligand (*Table 4.08*, *entry 1*). Using BIP **1.35**, silane **4.68** was observed in 84% yield, providing a benchmark for the comparison of all other ligands (*entry 2*). With TMEDA, silane **4.68** was produced in an equally excellent yield, whereas alternative bis(amine) ligands 2,2'-bipyridyl and 1,10-phenanthroline were not as effective as TMEDA and silane **4.68** was observed in lower yield (*entries 3-5*). As TMEDA is readily available and can be used as purchased, it was decided to perform future hydrofunctionalisations with this ligand.

BIP and TMEDA have significantly different properties and thus the role of the two ligands in the reaction may be different. BIP is a redox-active ligand able to accept electron density from a metal centre (*Scheme 4.12*),[73-76] and this property has led to many applications of BIP in iron catalysis, including the polymerisation and hydrosilylation of alkenes.[69-72]



Scheme 4.12. Redox activity of BIP in iron complexes

In comparison, TMEDA has found widespread application in the iron-catalysed cross-coupling reactions of Grignard reagents with organohalides. In some cases, the intended product was not observed unless TMEDA was used as an additive (*Scheme 4.13*).[264] TMEDA is proposed to suppress side reactions, when used both in stoichiometric and catalytic amounts.[265]

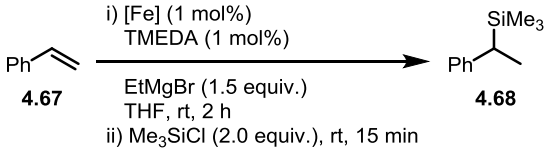


Scheme 4.13. Effect of additive on reaction outcome

In our case, although no observable side reactions occur, 50% of the starting material was recovered in the absence of ligand, suggesting that the lifetime of the catalyst is shorter than the time needed for 100% conversion of the starting material. Therefore, whilst TMEDA may not be needed to suppress unwanted side reactions, it may help to prolong the life of the catalyst.

All other reagents and reaction conditions were then screened in a bid to further improve the operational simplicity of the reaction.

Firstly, different iron salts were investigated. Even though anhydrous $FeCl_2$ is relatively inexpensive, iron hydrate salts are even more so and therefore various iron hydrate salts were screened (*Table 4.09*). Iron(II) chloride tetrahydrate and iron(III) chloride hexahydrate gave silane **4.68** in equally excellent yields, even though iron is in a different oxidation state in the precatalysts; however, owing to the deliquescent nature of iron(III) chloride hexahydrate, it was decided to use iron(II) chloride tetrahydrate as the iron precatalyst in future reactions.



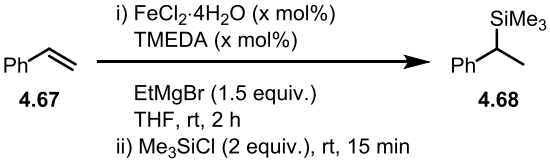
4.67 4.68

Entry	[Fe]	Yield (%)[a]
1	$FeCl_2$	92
2	$FeCl_2 \cdot 4H_2O$	92
3	$FeCl_3 \cdot 6H_2O$	89

[a] yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard

Table 4.09. Iron salt optimisation

The catalyst loading was screened and when the catalyst loading was lowered to 0.5 mol%, the yield was comparable to that obtained using 1 mol% (*Table 4.10, entries 1 and 2*). Decreasing this in 0.1 mol% increments was tolerated until the loading reached 0.1 mol% (*entries 3-6*), with a substantially reduced yield obtained in this case. This could not be improved by increasing the ligand loading fivefold with respect to iron salt (*entry 7*). In order to ensure an efficient hydromagnesiation, it was decided to use 0.5 mol% catalyst loading in future reactions.



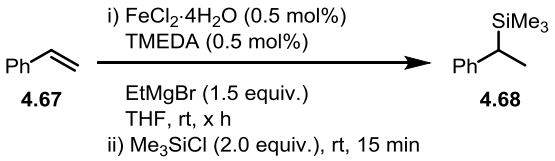
4.67 4.68

Entry	$FeCl_2 \cdot 4H_2O$ (mol%)	Ligand (mol%)	Yield (%)[a]
1	1	1	92
2	0.5	0.5	91
3	0.4	0.4	87
4	0.3	0.3	89
5	0.2	0.2	86
6	0.1	0.1	59
7	0.1	0.5	62

[a] yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard

Table 4.10. Catalyst loading optimisation

Next, the length of time of the hydromagnesiation step was examined (*Table 4.11*). After thirty minutes only 17% of styrene had undergone hydromagnesiation (assuming all benzylic Grignard intermediate is converted to silane), compared to 79% after one hour (*Table 4.11, entries 1 and 2*). Marginal increases in yield were observed when the hydromagnesiation step was further extended until the reaction was more or less quantitative after a two hour hydromagnesiation (*entries 3 and 4*).

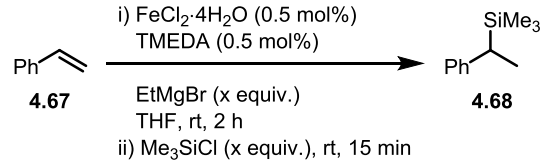


Entry	Hydromagnesiation time (h)	Yield 4.68 (%)[a]
1	0.5	17 (43% **4.67**)
2	1.0	79 (20% **4.67**)
3	1.5	89
4	2.0	95

[a] yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard

Table 4.11. Hydromagnesiation time optimisation

It was also hoped to reduce the number of equivalents of ethylmagnesium bromide and electrophile required (*Table 4.12*) (the electrophile must always be in excess with respect to ethylmagnesium bromide, owing to a competitive reaction between the two reagents). Unfortunately, the amount of ethylmagnesium bromide could not be reduced below 1.5 equivalents without compromising the yield of the reaction.

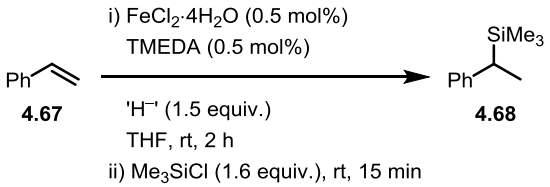


Entry	EtMgBr (equiv.)	$SiMe_3Cl$ (equiv.)	Yield (%)[a]
1	1.1	1.2	74
2	1.2	1.3	72
3	1.3	1.4	83
4	1.4	1.5	83
5	1.5	1.6	95

[a] yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard

Table 4.12. Equivalents of Grignard reagent and electrophile optimisation

Other hydride sources, in addition to ethylmagnesium bromide, were also screened in order to determine whether this reaction could be extended to other hydrometalations (*Table 4.13*). Also, if the hydrofunctionalisation was ultimately to be rendered enantioselective, this might be more feasible with another metal, as the rate of benzylic Grignard reagent racemisation is appreciable at room temperature.[266] No hydrometallation was observed with any alternative hydride source; with *n*-BuLi the starting material was completely consumed and nothing could be identified in the crude ^{1}H NMR spectra of the reaction mixtures, suggesting polymerisation (*Table 4.13, entry 3*).



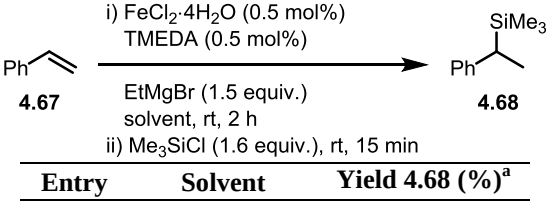
4.67 **4.68**

Entry	'H^-'	Yield 4.68 (%)[a]
1	EtMgBr	95
2	$NaHBEt_3$	0 (35% **4.67**)
3	*n*-BuLi	0
4	Et_2Zn	0 (91% **4.67**)
5	L-selectride®	0 (96% **4.67**)

[a] yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard

Table 4.13. Screening with alternative hydride sources

Alternative solvents that are more industrially favoured compared with THF were also investigated (*Table 4.14*).[267] TBME (*t*-butylmethyl ether) and 2-MeTHF were screened, in addition to diethyl ether and toluene (*Table 4.14, entries 3-6*). Unfortunately, no product was observed when the reaction was conducted in any solvent other than THF and differing amounts of starting material were recovered in each case. It was also found that the reaction could be performed in "wet" THF, further enhancing the operational simplicity of the reaction (*entry 2*).



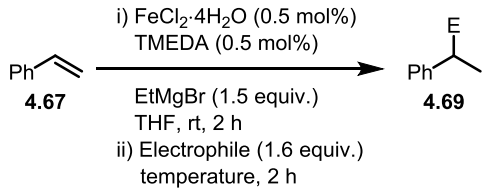
4.67 **4.68**

Entry	Solvent	Yield 4.68 (%)[a]
1	THF	92
2	"wet" THF[b]	91
3	TBME	0 (44% **4.67**)
4	2-MeTHF	0 (48% **4.67**)
5	Et_2O	0 (83% **4.67**)
6	toluene	0 (29% **4.67**)

[a] yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard
[b] 3-methoxystyrene used as substrate and THF used with no prior purification

Table 4.14. Solvent optimisation

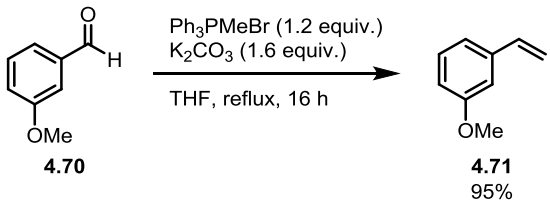
With the optimised hydrofunctionalisation conditions in hand (*Scheme 4.14*), focus turned to the electrophile scope and firstly, carbon electrophiles.



Scheme 4.14. Optimal hydrofunctionalisation conditions

4.2.3 Carbon Electrophile Scope

3-Methoxystyrene **4.71** was used as the model substrate, as in contrast to styrene, this could be visualised by UV light upon TLC analysis. 3-Methoxystyrene **4.71** was synthesised by a Wittig reaction,[268-269] from *m*-anisaldehyde **4.70** and methyltriphenylphosphonium bromide in 95% yield (*Scheme 4.15*).[226]



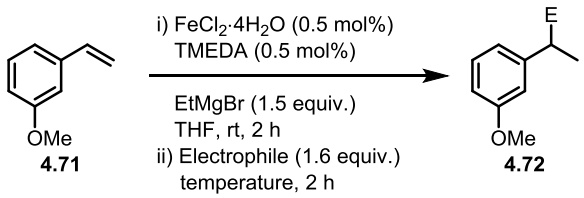
Scheme 4.15. Synthesis of 3-methoxystyrene **4.71**

Next, a series of carbon electrophiles were screened in the hope of synthesising a range of carbon–carbon bonds. After addition of the electrophile, the reaction was left for two hours in order to ensure complete reaction of the *in situ* prepared Grignard reagent. This was especially important for those reactions in which the electrophile was added at −78 °C. Where possible the electrophile was added to the Grignard intermediate, in order to ensure operational simplicity. However, in cases where the electrophile was insoluble in THF, the benzylic Grignard intermediate was added to a 1 M suspension of the electrophile in THF *via* cannula.

4.2.3.1 S_N2 Susceptible and Cationic Electrophiles

First, a series of alkyl halide electrophiles were screened (*Table 4.15*). The reaction with allyl bromide **4.73** was successful giving alkene **4.74** in excellent yield (*Table 4.15, entry 1*). Similarly, the reactions with benzyl bromide **4.75** and benzyl chloride **4.77** were high yielding (e*ntries 2 and 3*); in both cases the benzylic Grignard intermediate was cooled to −78 °C prior to addition of the electrophile in order to suppress competing oxidative

homocoupling of the Grignard intermediate. Functionalised benzyl bromide **4.78** gave **4.79** in a moderate 54% yield owing to significant reductive homocoupling of the electrophile (*entry 4*). Nevertheless the ester functionality remained intact, highlighting the chemoselective nature of the addition. 1-Chloro-3-iodopropane **4.80** underwent a chemoselective S_N2 reaction at iodine and alkane **4.81** was isolated in 62% yield (*entry 5*).



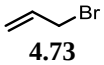
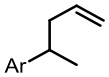
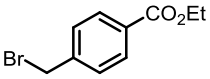
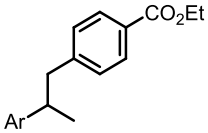
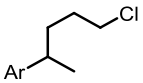
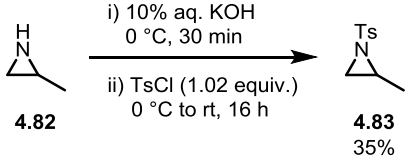
Entry	Temperature	Electrophile	Product	Yield (%)
1	rt	 **4.73**	 **4.74**	81
2	−78 °C	 **4.75**	 **4.76**	85
3	−78 °C	 **4.77**	 **4.76**	91
4	−78 °C	 **4.78**	 **4.79**	54
5	rt	 **4.80**	 **4.81**	62

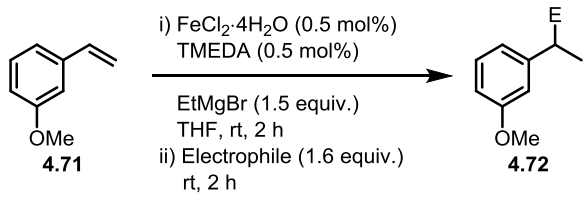
Table 4.15. Alkyl halide electrophiles

The electrophile scope was also extended to the ring-opening of aziridines and epoxides (*Table 4.16*). An unprotected aziridine would be susceptible to deprotonation by the Grignard reagent and so 2-methylaziridine **4.82** was first protected with a tosyl group to give *N*-tosylaziridine **4.83** (*Scheme 4.16*).[270]



Scheme 4.16. Synthesis of *N*-tosylaziridine **4.83**

Racemic *N*-tosylaziridine **4.83** was regioselectively ring-opened at the least-substituted carbon and amine **4.84** was isolated in excellent yield as a 1:1 mixture of diastereomers (*Table 4.16, entry 1*). Epoxides **4.85** and **4.87** also underwent regioselective ring-opening in excellent yield with enantioenriched epoxide **4.87** giving alcohol **4.88** as a 1:1 mixture of diastereomers (racemic at the benzylic carbon) (*entries 2 and 3*).



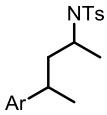
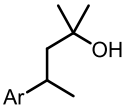
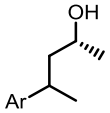
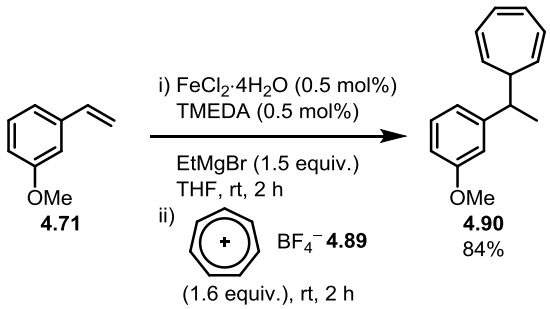
Entry	Electrophile	Product	Yield (%)
1	 **4.83**	 1:1 *dr* **4.84**	78
2	 **4.85**	 **4.86**	70
3	 **4.87**	 1:1 *dr* **4.88**	71

Table 4.16. Ring opening of epoxides and aziridines

Tropylium tetrafluoroborate **4.89** was also trapped successfully to give triene **4.90** in 84% yield (*Scheme 4.17*). In this case, the Grignard intermediate was added *via* cannula to a 1 M suspension of **4.89** in THF, owing to the low solubility of the electrophile in THF.



Scheme 4.17. Trapping of tropylium tetrafluoroborate **4.89**

Following the success with S_N2 susceptible and cationic electrophiles, attention turned to

carbonyl electrophiles.

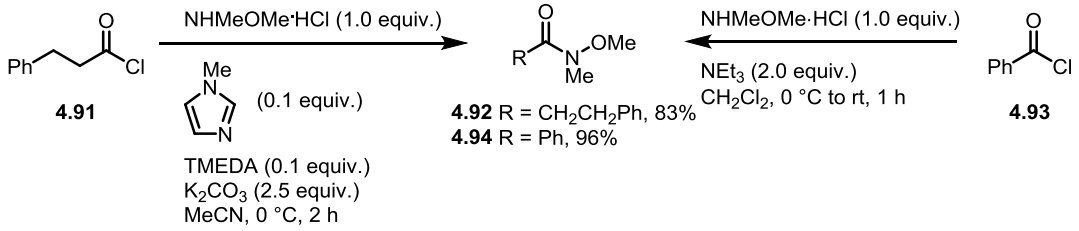
4.2.3.2 Carbonyl Electrophiles

The reaction of Grignard reagents with carbonyl compounds has been well studied over the years and is an established method for the preparation of secondary and tertiary alcohols, amongst other functionalised products.[229, 271]

It was hoped that the benzylic Grignard reagent would react with a range of carbonyl electrophiles. The majority of carbonyl electrophiles tested were readily available in the laboratory but some were synthesised.

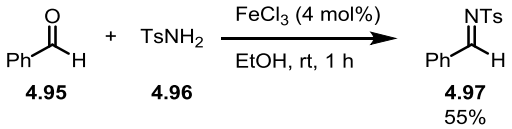
4.2.3.2.1 Synthesis

Ketones were targeted using Weinreb amides;[272] alkyl Weinreb amide **4.92** was prepared from *N,O*-dimethylhydroxylamine hydrochloride and hydrocinnamoyl chloride **4.91** in 83% yield,[273] and phenyl Weinreb amide **4.94** from the same amine salt and benzoyl chloride **4.93** in an equally excellent 96% yield (*Scheme 4.18*).[274]



Scheme 4.18. Synthesis of Weinreb amides **4.92** and **4.94**

Imine electrophiles were explored as a route to amines and aldimine **4.97** was prepared from benzaldehyde **4.95** and *p*-toluenesulfonamide **4.96** using iron catalysis (*Scheme 4.19*).[275]

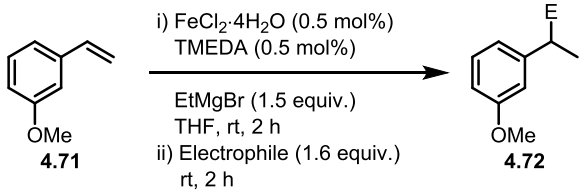


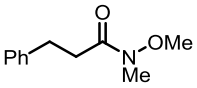
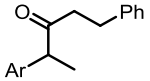
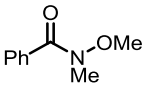
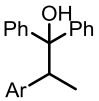
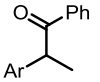
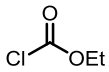
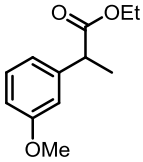
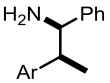
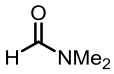
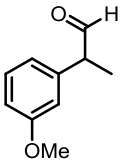
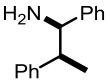
Scheme 4.19. Synthesis of aldimine **4.97**

4.2.3.2.2 Reaction

A range of carbonyl electrophiles were tested (*Table 4.17*). The reactions with benzaldehyde **4.95** and paraformaldehyde **4.98** resulted in complex mixtures of products in the ^{1}H NMR spectra of the crude reaction mixtures (*Table 4.17, entries 1 and 2*). However, the absence of

product for paraformaldehyde **4.98** could be owing to the lack of formaldehyde monomers present in solution. The reaction with benzophenone **4.99** was more successful and tertiary alcohol **4.100** was observed in 25% yield (*entry 3*).



Entry	Electrophile	Product	Yield (%)	Entry	Electrophile	Product	Yield (%)
1	PhCHO **4.95**	complex mixture	-	7	 **4.92**	 **4.105**	22[a]
2	$(HCHO)_n$ **4.98**	complex mixture	-	8	 **4.94**	 **4.106**	24[a]
3	PhCOPh **4.99**	 **4.100**	25%[a, b]	9	PhCN **4.107**	 **4.106**	65
4	 **4.101**	 **4.102**	75	10	PhCN **4.107** then MeOH, $NaBH_4$	 **(±)-4.108**	55
5	 **4.103**	 **4.104**	64	11	PhCN **4.107** then MeOH, $NaBH_4$	 **(±)-4.109**[c]	39[a]
6	PhCOCl **4.93**	complex mixture		12	 **4.97**	complex mixture	-

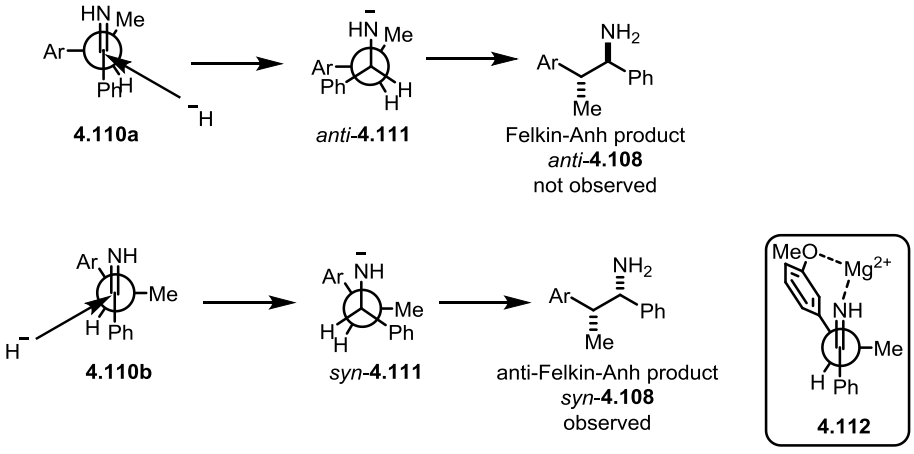
[a] yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard
[b] benzophenone added at −78 °C
[c] styrene used as substrate

Table 4.17. Carbonyl electrophiles

Pleasingly, the reactions with ethyl chloroformate **4.101** and *N*,*N*-dimethylformamide (DMF) **4.103** were both high yielding and ester **4.102** and aldehyde **4.104** were isolated in 75% and 64% yield respectively (*entries 4 and 5*). Significantly, the ester functionality remained intact even though an excess of ethylmagnesium bromide was used in the hydromagnesiation. Initially, ketones were targeted from acid chlorides and Weinreb amides

(*entries 6-8*).

No successful reaction occurred with benzoyl chloride **4.93** and the reactions with Weinreb amides **4.92** and **4.94** were poor yielding, with the respective ketones **4.105** and **4.106** observed in 22% and 24% yield. The poor yield for aryl Weinreb amide **4.94** was somewhat surprising, which in contrast to alkyl Weinreb amide **4.92**, lacks acidic protons α to the carbonyl group. However, phenyl ketone **4.106** could be accessed using benzonitrile **4.107**, with the imine intermediate hydrolysed on work-up to reveal phenyl ketone **4.106** in 65% yield (*entry 9*). The imine intermediate was also reduced to amine **4.108** with sodium borohydride (*entry 10*); interestingly amine **4.108** was produced as a single diastereomer—a racemic mixture of *syn* diastereomers by comparison with ^{1}H NMR spectra of the *syn* and *anti* diastereomers in the literature.[276-277] Using the Felkin-Anh model[278-280] and positioning the larger phenyl group perpendicular to the imine (**4.110a**) gives *anti*-**4.108**, which is the opposite stereochemical outcome to that observed (*Scheme 4.20*). *Syn*-**4.108** is predicted only if the methyl group is positioned perpendicular to the imine (**4.110b**) and this conformation could be preferred if the methoxy substituent on the aryl ring was chelating to a magnesium ion present in solution (**4.112**). However, chelate **4.112** would be eight-membered and thus may be challenging to form. To test this hypothesis the reaction was repeated using styrene and *syn*-**4.109** was observed, suggesting that chelation control was not responsible for the stereochemical outcome of the reaction (*Table 4.17, Entry 11*).



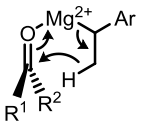
Scheme 4.20. Felkin-Anh model for the reduction of imine **4.110**

In contrast, when aldimine **4.97** was used in the reaction in the hope of accessing the corresponding *N*-tosyl amine, no reaction occurred (*Entry 12*). The reductive animation strategy thus offers an alternative route to amines and since *N*-tosyl group deprotection generally requires harsh conditions[281] this is perhaps a more versatile strategy.

At present, the difference in reactivity between carbonyl electrophiles is difficult to explain. One possible explanation invokes the HOMO of the benzylic Grignard reagent and the LUMO of the carbonyl electrophile.[282] Grignard reagents are known to be hard nucleophiles and thus have a low energy HOMO. A hard nucleophile with a low energy HOMO is generally reactive towards hard electrophiles with high energy LUMOs and this reactivity is governed by a large Coulombic attraction between the two species. Esters and amides are known to have higher energy LUMOs than aldehydes and ketones by virtue of the oxygen and nitrogen lone pair conjugation with the carbonyl group. Therefore, esters and amides are harder electrophiles than aldehydes and ketones and the reactions with the benzylic Grignard reagent are more successful.

A simpler explanation is that the less reactive carbonyl electrophiles (e.g. esters and amides) are more compatible with the harsh reaction conditions whereas the more reactive carbonyl electrophiles (e.g. aldehydes and ketones) decompose under the reaction conditions. Radical-mediated side reactions, such as pinacol coupling[283] and the McMurry reaction,[284] could account for the low yields observed when using reactive carbonyl electrophiles in the presence of metals.

It is noteworthy that no products arising from the Meerwein-Ponndorf Verley reduction[285-286] of the carbonyl electrophiles were observed (*Scheme 4.21*).

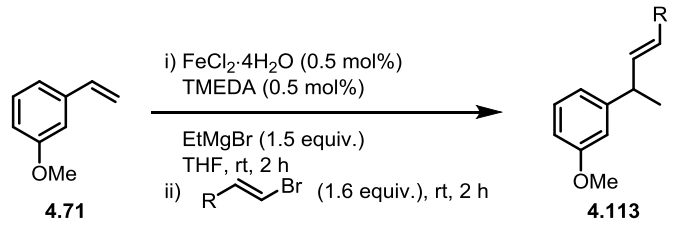


Scheme 4.21. Meerwein-Ponndorf Verley reduction of carbonyls

4.2.3.3 Formal Cross-Coupling

Using alkenyl halide electrophiles, the products of formal cross-coupling reactions were

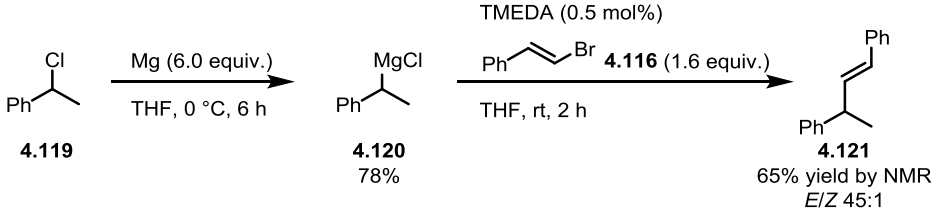
obtained (*Table 4.18*). With vinyl bromide **4.114**, alkene **4.115** was isolated in 76% yield (*Table 4.18, entry 1*). The reaction with *β*-bromostyrene **4.116** gave (*E*)-styrene derivative **4.117** in 78% yield with complete stereoretention (*entry 2*). Interestingly, the same product was obtained with *α*-bromostyrene **4.118** as that with *β*-bromostyrene **4.116**, albeit as a 1:1 mixture of *E*/*Z* isomers (*entry 3*).



Entry	Alkenyl halide	Product	Yield (%)
1	**4.114**	**4.115**	76
2	*E*:*Z* 11:1 **4.116**	*E*/*Z* 13:1 **4.117**	78
3	**4.118**	*E*/*Z* 1:1 **4.117**	64

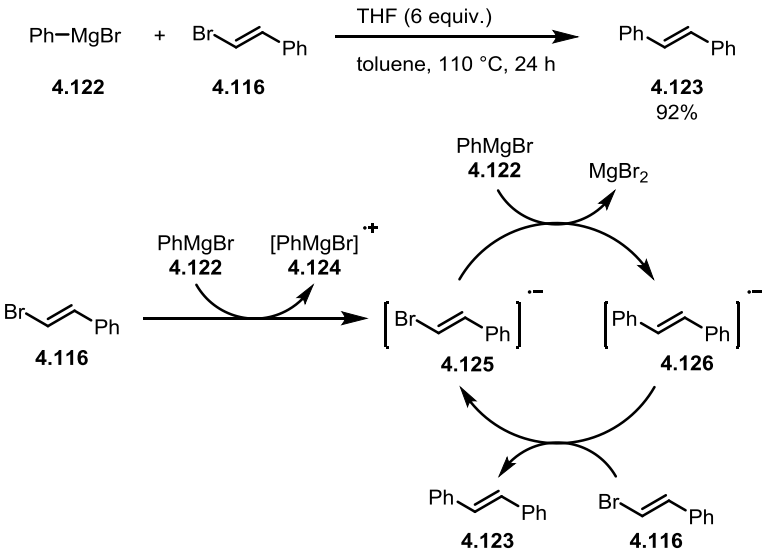
Table 4.18. Formal cross-coupling with alkenyl halides

In order to explore whether the cross-coupling was iron-catalysed, the reaction was performed in the absence of iron. Another PhD student in the group, James Paliga, prepared benzylic Grignard reagent **4.120** independently from (1-chloroethyl)benzene **4.119** and magnesium,[266] which was then reacted with *β*-bromostyrene **4.116** in the presence of TMEDA (*Scheme 4.22*). Styrene derivative **4.121** was observed in 65% yield by ^{1}H NMR spectroscopy, comparable to the 78% obtained in the presence of iron.



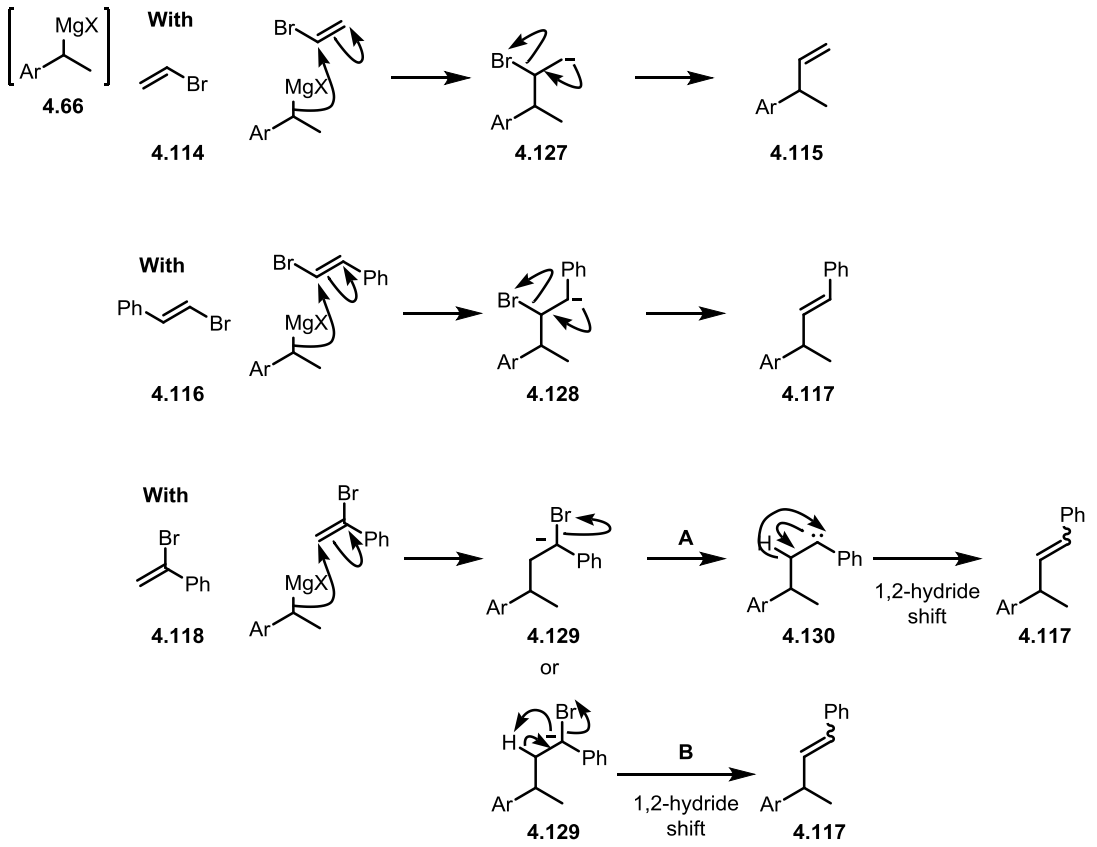
Scheme 4.22. Reaction of independently prepared Grignard reagent **4.120** with *β*-bromostyrene **4.116**

Shirakawa and Hayashi recently reported the metal-free single-electron transfer-induced cross-coupling reaction of aryl Grignard reagents with alkenyl halides.[287] When *β*-bromostyrene **4.116** was used, (*E*)-stilbene **4.123** was isolated in 92% yield and significantly the reaction was stereospecific (*Scheme 4.23*). A single-electron transfer mechanism was proposed based on earlier work on the cross-coupling of aryl Grignard reagents with aryl halides.[288] As the reaction was stereospecific, the mechanism proposed does not involve an alkenyl radical, which would be subject to racemisation.[289-290] Initiation through single-electron transfer from phenylmagnesium bromide **4.122** to *β*-bromostyrene **4.116** gives anionic radical **4.125**. Direct C–C bond formation of **4.125** with phenylmagnesium bromide **4.122** gives **4.126**, which then transfers an electron to another molecule of *β*-bromostyrene **4.116** to complete the catalytic cycle and release (*E*)-stilbene **4.123**.



Scheme 4.23. Metal-free cross coupling by Shirakawa and Hayashi

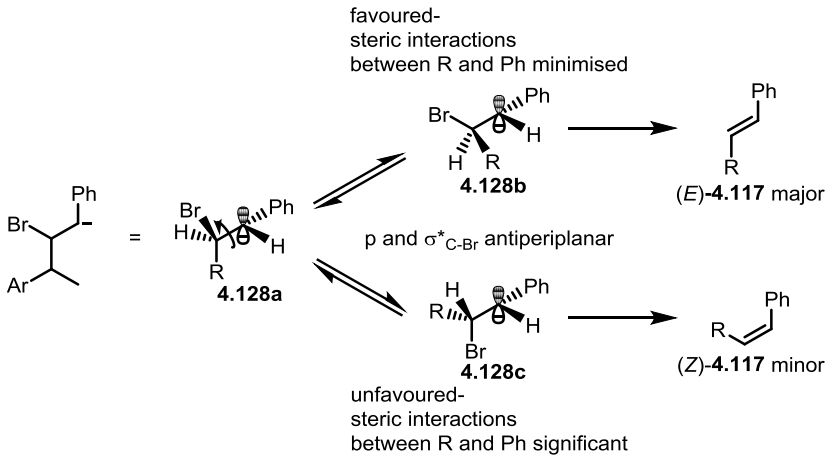
The cross-coupling of the benzylic Grignard intermediate with *β*-bromostyrene **4.116** may proceed through a similar single-electron transfer mechanism, especially as the reaction was stereospecific, and thus may not necessarily be iron-catalysed. Another mechanistic possibility, for all vinyl halide electrophiles, would involve an addition-elimination mechanism (*Scheme 4.24*).



Scheme 4.24. Addition-elimination mechanism with vinyl halide electrophiles

Initial addition of benzylic Grignard reagent **4.66** to vinyl bromide **4.114** and *β*-bromostyrene **4.116** would lead to carbanions **4.127** and **4.128**, respectively. Benzylic carbanion **4.128** is stabilised through conjugation with the phenyl ring whereas carbanion **4.127** is unstabilised. However, even though carbanion **4.127** is unstabilised, vinyl bromide **4.114** has been used before in S_N2-like reactions.[291]

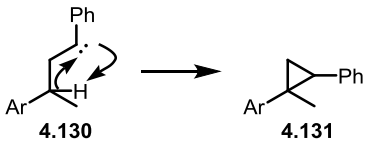
This mechanism is consistent with the 13:1 mixture of *E*/*Z* alkene **4.117** isomers obtained in the reaction with *β*-bromostyrene **4.116**. (*Scheme 4.25*). Rotation about the central C–C bond in anion **4.128a** leads to conformers **4.128b** and **4.128c** in which the p and σ^*_{C-Br} orbitals are antiperiplanar—the necessary conformation for elimination of bromide. In anion **4.128b** the R and Ph groups are *anti* whereas in anion **4.128c** the groups are *syn*; the *anti* arrangement minimises the steric interactions between the groups, making anion **4.128b** the favoured conformation and thus alkene (*E*)-**4.117** the major stereoisomeric product.



Scheme 4.25. Stereochemical outcome for reaction with *β*-bromostyrene **4.116**

With *α*-bromostyrene **4.118**, addition of the Grignard reagent at the *β* position would lead to carbanion **4.129**, which is both stabilised mesomerically through conjugation with the phenyl ring and inductively by bromine. Two routes to styrene derivative **4.117** could now be envisaged. Route **A** involves the loss of bromide to give carbene **4.130**, which subsequently undergoes a 1,2-hydride shift, to reform the double bond, whereas route **B** involves a direct 1,2-hydride shift with concurrent loss of bromide.

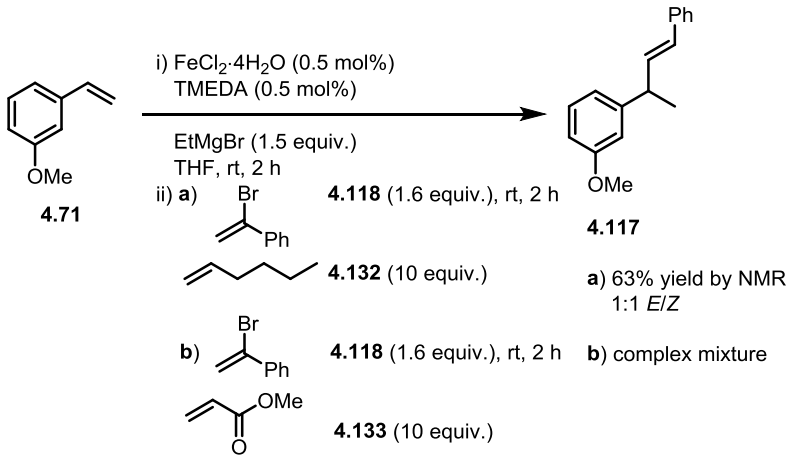
Cyclopropane **4.131** could result from a C–H insertion reaction into the benzylic most acidic proton of carbene intermediate **4.130** but was not observed in ^{1}H NMR spectrum of the crude reaction mixture (*Scheme 4.26*).



Scheme 4.26. C–H insertion leading to cyclopropane **4.131**

To further investigate the presence of a carbene intermediate, the reaction with *α*-bromostyrene **4.118** was performed in the presence of an alkene, with the intention of trapping the carbene with the alkene to form a cyclopropane. Using 10 equivalents of alkene, as the rate of intramolecular rearrangement is likely to be faster than intermolecular trapping, an electron-rich alkene (**4.132**) and an electron-poor alkene (**4.133**) were explored (*Scheme 4.27*). No cyclopropanes were observed in the ^{1}H NMR spectra of the crude reaction mixtures using 1-hexene **4.132** or methyl acrylate **4.133** (these alkenes have

previously been used to trap carbenes).[292] However, this does not rule out the possibility of a carbene intermediate, as the rate of intramolecular rearrangement could be significantly faster than the rate of carbene trapping.

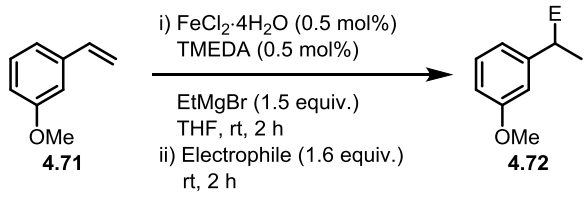


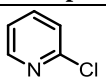
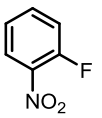
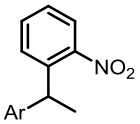
Scheme 4.27. Carbene intermediate exploration

Different mechanisms for each vinyl halide electrophile may also be operating. Although at present the mechanism operating for each vinyl halide electrophile has not been determined, the single-electron transfer mechanism discussed seems most plausible.[287]

4.2.3.4 Aryl Electrophiles

2-Chloropyridine **4.134** and 1-fluoro-2-nitrobenzene **4.135** were screened as electrophiles that could participate in S_NAr reactions (*Table 4.119*).



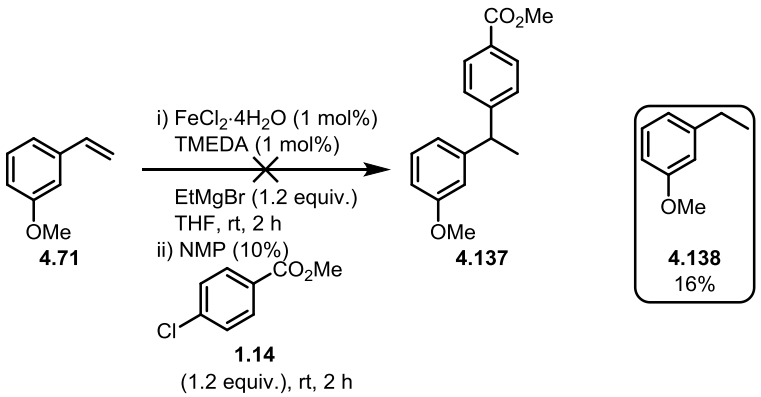
Entry	Electrophile	Product	Yield (%)[a]
1	 **4.134**	Complex mixture	-
2	 **4.135**	 **4.136**	4

[a] yield determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard

Table 4.19. S_NAr electrophiles

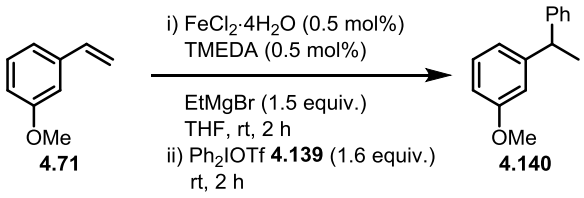
No product was observed in the reaction with 2-chloropyridine **4.134** and only a 4% yield by

^{1}H NMR spectroscopy was observed for 1-fluoro-2-nitrobenzene **4.135**, suggesting low reactivity with these electrophiles. Next, a series of aryl electrophiles were explored in the hope of performing iron-catalysed cross-coupling reactions. Methyl 4-chlorobenzoate **1.14** was selected as the model cross-coupling partner owing to the good reactivity of the electrophile in previous iron-catalysed cross-coupling reactions (see *section 1.1.1.2*).[39] Following the preparation of the benzylic Grignard reagent (in 5 mL THF), 0.5 mL (10% by volume) of NMP was added to the reaction in order to prevent catalyst decomposition, possibly by *β*-hydride elimination of the Grignard reagent,[293] to which aryl chloride **1.14** was added (*Scheme 4.28*). No cross-coupling occurred—only 16% ethylbenzene derivative **4.138** and 10% starting material **4.71** were visible in the ^{1}H NMR spectrum (ethylbenzene derivative **4.138** resulting from protonation of the benzylic Grignard intermediate).



Scheme 4.28. Unsuccessful cross-coupling reaction with aryl chloride **1.14**

Next, diphenyliodonium triflate **4.139** was investigated (*Table 4.20*), which had been used in the copper-catalysed arylation of a variety of nucleophiles.[294] Iodonium **4.139** was added as a 0.2 M solution in THF unless otherwise stated. Directly adding iodonium **4.139** to the benzylic Grignard reagent gave arylated product in 10% yield by ^{1}H NMR spectroscopy (*Table 4.20, entry 1*). Owing to iodonium **4.139** being only sparingly soluble in THF, **4.139** was next added in DCE, as good reactivity with this reagent had been previously observed by Gaunt and co-workers when using DCE.[295] With DCE, product **4.140** was observed in comparable yield to that obtained using THF and it was noted that iodonium **4.139** was also not fully soluble in DCE (*entry 2*).

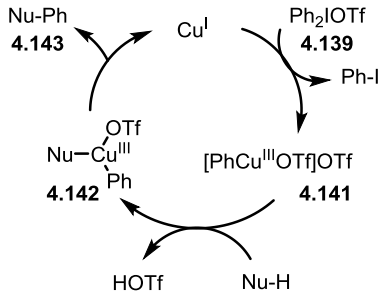


Entry	Conditions	Yield (%)[a]
1	-	10
2	Iodonium added as a 0.2 M DCE solution	9
3	Benzylic Grignard intermediate added to iodonium and $FeCl_2 \cdot 4H_2O$ (5 mol%)	4
4	Benzylic Grignard intermediate added to iodonium and CuCl (5 mol%)	8
5	Benzylic Grignard intermediate added to iodonium and $Cu(OTf)_2$ (5 mol%)	3

[a] yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard

Table 4.20. Attempted cross-coupling with diphenyliodonium triflate **4.139**

Adding the benzylic Grignard reagent to a solution of iodonium **4.139** in the presence of either an iron or copper salt was also not beneficial and a lower yield of product was observed in each case (*entries 3-5*). Gaunt and co-workers suggested that Cu(I) undergoes oxidative addition with diphenyliodonium **4.139** to give electrophilic Cu(III) species **4.141** (*Scheme 4.29*). Attack by a nucleophile gives **4.142**, which after reductive elimination, gives arylated product **4.143** and regenerates the Cu(I) catalyst. Interestingly in this work, a Cu(II) pre-catalyst can be used, which is reduced *in situ* to give the active Cu(I) catalyst.[294]

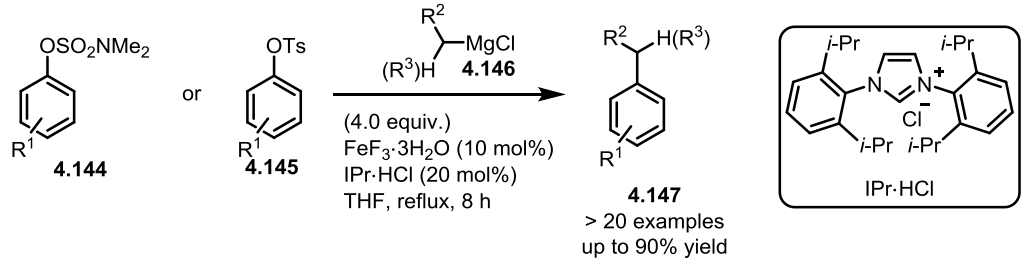


Scheme 4.29. Copper-catalysed arylation of nucleophiles

A report was later found that stated diphenyliodonium salts react with alkyl Grignard reagents to give a complex mixture of products containing iodobenzene as the major product,[296] so it is perhaps not surprising that the intended product was only formed in low yield.

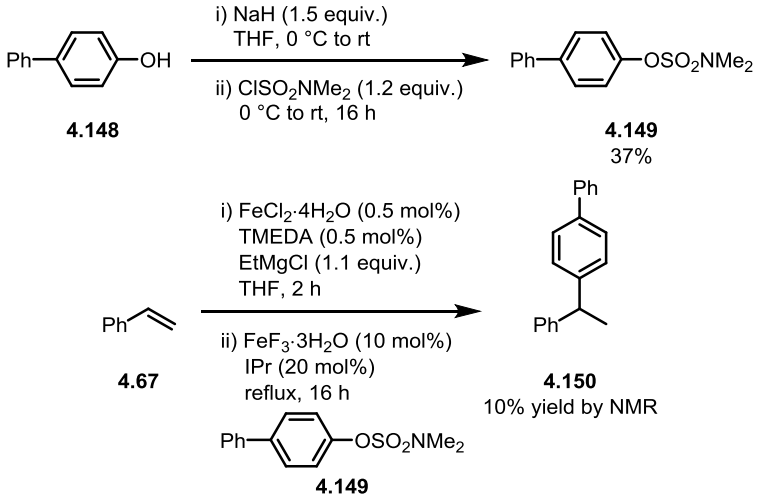
Agrawal and Cook recently reported the iron-catalysed cross-coupling of alkyl Grignard reagents **4.146** with aryl sulfamates **4.144** and tosylates **4.145** using $FeF_3 \cdot 3H_2O$ and NHC

ligand IPr (*Scheme 4.30*).[297]



Scheme 4.30. Iron-catalysed cross-coupling of alkyl Grignard reagents with aryl sulfamates and tosylates

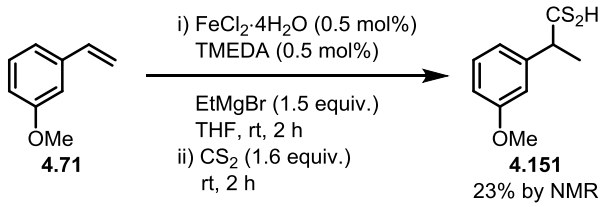
It was hoped that these conditions could be applied to the cross-coupling of the *in situ* prepared benzylic Grignard reagent with an aryl sulfamate. Aryl sulfamate **4.149** was first synthesised from 4-phenylphenol **4.148** and *N*,*N*-dimethylsulfamoyl chloride (*Scheme 4.31*),[297] which was then subjected to cross-coupling. Only a 10% yield by ^{1}H NMR spectroscopy was observed and so, after a few unsuccessful attempts at forming carbon–aryl bonds, it was decided to focus on other electrophiles.



Scheme 4.31. Synthesis of aryl sulfamate **4.149** and cross-coupling

4.2.3.5 Carbon Disulfide

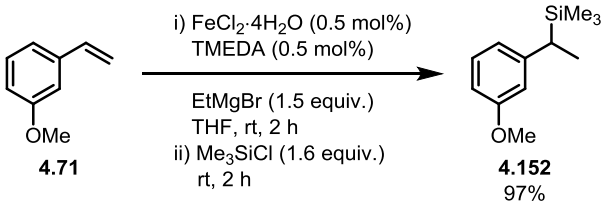
Owing to the number of styrene derivatives that underwent hydrocarboxylation,[226] the reaction was performed with the sulfur analogue of carbon dioxide, carbon disulfide (*Scheme 4.32*), but only a 23% yield by ^{1}H NMR spectroscopy of dithioic acid **4.151** was detected. Carbon disulfide is more reactive than carbon dioxide and thus, like the more reactive carbonyl electrophiles investigated, may decompose under the reaction conditions.



Scheme 4.32. Reaction with carbon disulfide

4.2.4 Heteroatom Electrophile Scope

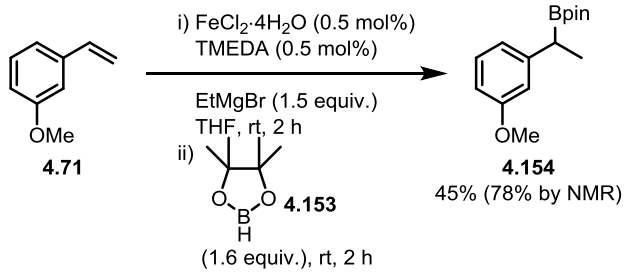
Attention then turned to the heteroatom electrophile scope. Following the successful trapping of trimethylsilyl chloride with the benzylic Grignard reagent (*Scheme 4.33*), a range of heteronuclear electrophiles were explored.



Scheme 4.33. Reaction with trimethylsilyl chloride

4.2.4.1 Formal Hydroboration

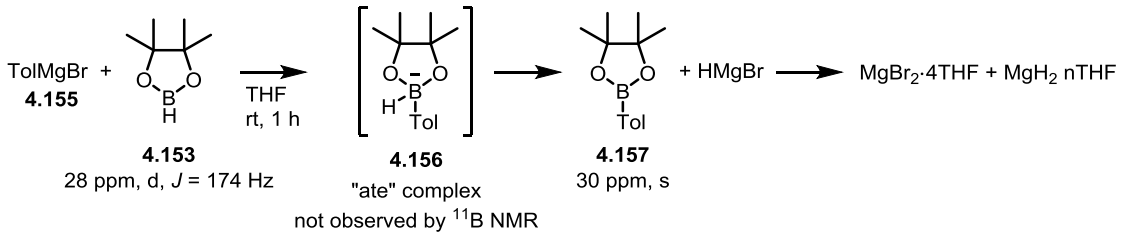
When pinacolborane **4.153** was used in the reaction, boronic ester **4.154** was observed in 78% by ^{1}H NMR spectroscopy (*Scheme 4.34*). Even though a 78% yield by ^{1}H NMR spectroscopy was detected, boronic ester **4.154** was only isolated in 45% yield and this was attributed to low product stability on silica gel (Wang and co-workers reported a similar significantly lower yield of boronic ester **4.154** following purification by column chromatography on silica gel[298]).



Scheme 4.34. Formal hydroboration of styrene **4.71**

The reaction with pinacolborane was thought to occur with hydride acting as the leaving group, as previously reported by Singaram and co-workers (*Scheme 4.35*).[299] Although "ate" complex **4.156** was not observed by ^{11}B NMR spectroscopy, a crystal structure of

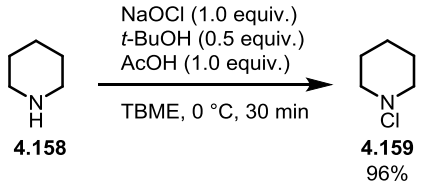
$MgBr_2 \cdot 4THF$ was obtained, which was postulated to originate from the rearrangement of HMgBr to $MgBr_2$ and MgH_2. MgH_2 was subsequently reacted with borane and the adduct characterised by ^{11}B NMR spectroscopy.



Scheme 4.35. Hydride as a leaving group in reaction of Grignard reagent **4.155** with pinacol borane **4.153**

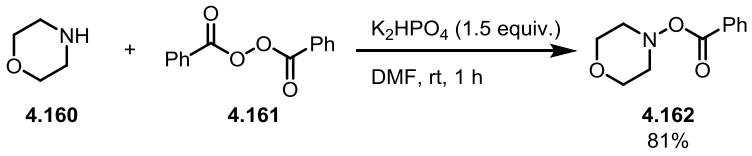
4.2.4.2 Nitrogen and Phosphorus Electrophiles

A range of nitrogen electrophiles were next examined in the hope of forming a series of carbon–nitrogen bonds. *N*-Chloropiperidine **4.159** was prepared from piperidine **4.158** and sodium hypochlorite in 96% yield after a simple aqueous work-up (*Scheme 4.36*).[300]



Scheme 4.36. Synthesis of *N*-chloropiperidine **4.159**

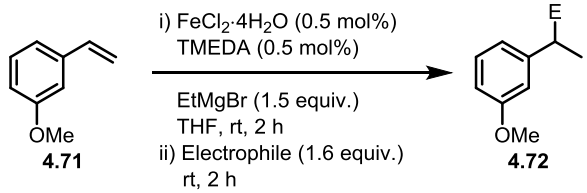
Morpholine derivative **4.162** was accessed from morpholine **4.160** and benzoyl peroxide **4.161** in 81% yield (*Scheme 4.37*).[301]

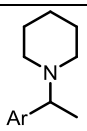
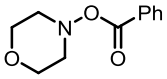
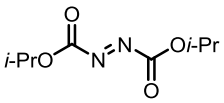


Scheme 4.37. Synthesis of morpholine derivative **4.162**

With these two potential nitrogen electrophiles in hand, both were tested in the reaction, in addition to di-i*so*-propyl azodicarboxylate (DIAD) **4.165** and nitrosobenzene **4.166** (*Table 4.21*). *N*-Chloropiperidine **4.159** was the only successful nitrogen electrophile and gave amine **4.163** in a poor 6% yield by ^1H NMR spectroscopy (*Table 4.21, entry 1*). In the reaction with morpholine derivative **4.162**, the major product in the ^1H NMR spectrum was propiophenone **4.164**, originating from the addition of ethylmagnesium bromide to the

carbonyl functionality in the electrophile (*entry 2*). The ^{1}H NMR spectra for the reactions with DIAD **4.165** and nitrosobenzene **4.166** were complex and no discernible product could be identified (*entries 3 and 4*).

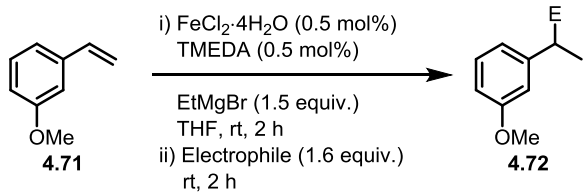


Entry	Electrophile	Product	Yield (%)[a]
1	 **4.159**	 **4.163**	6
2	 **4.162**	 **4.164**	19
3	 **4.165**	complex mixture	-
4	PhNO **4.166**	complex mixture	-

[a] yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard

Table 4.21. Nitrogen electrophiles

Attention then turned to phosphorus electrophiles and diphenylphosphinic chloride **4.167** and diethyl chlorophosphate **4.169** were added to the benzylic Grignard reagent (*Table 4.22*).



Entry	Electrophile	Product[a]	Yield (%)[a]
1	$Ph_2P(O)Cl$ **4.167**	$Ph_2P(O)Et$ **4.168**	39%
2	$(EtO)_2P(O)Cl$ **4.169**	complex mixture	-

[a] yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard

Table 4.22. Phosphorus electrophiles

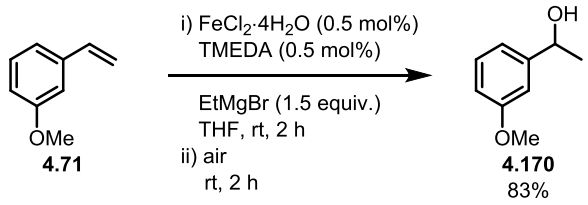
Neither phosphorus electrophile gave any of the intended products and the major product for phosphinic chloride **4.167** was $Ph_2P(O)Et$ **4.168** in 39% yield by ^{1}H NMR spectroscopy,

resulting from nucleophilic substitution by ethylmagnesium bromide.

4.2.4.3 Oxygen and Sulfur Electrophiles

The reaction of Grignard reagents with oxygen is well known and the preparation of Grignard reagents requires the exclusion of oxygen for this very reason.[229]

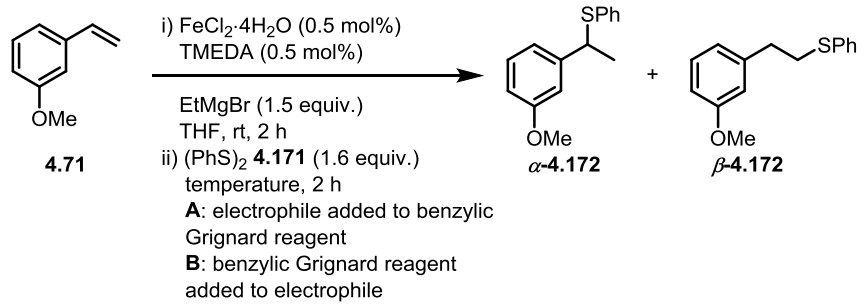
After the formation of the benzylic Grignard reagent, the reaction was opened to the atmosphere to react with oxygen and form alcohol **4.170** in 83% yield after work-up (*Scheme 4.38*). The reaction of Grignard reagents with oxygen is known to give peroxide species in a radical-based mechanism, which are subsequently hydrolysed upon work-up to reveal alcohols.[302]



Scheme 4.38. Exposure of reaction to air and formation of alcohol **4.170**

Three sulfur electrophiles were tested: diphenyl disulfide **4.171**, tosyl chloride **4.176** and 1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) (DABSO) adduct **4.178**.

With diphenyl disulfide **4.171**, sulfide **4.172** was obtained as a 22:1 mixture of α:β regioisomers (*Table 4.23, entry 1*). As diphenyl disulfide was the only electrophile with which an appreciable amount of β regioisomer formed, the addition temperature and method (whether the electrophile was added to the benzylic Grignard reagents or *vice versa*) were varied in order to explore the effect of these variables on the regioselectivity of the reaction.



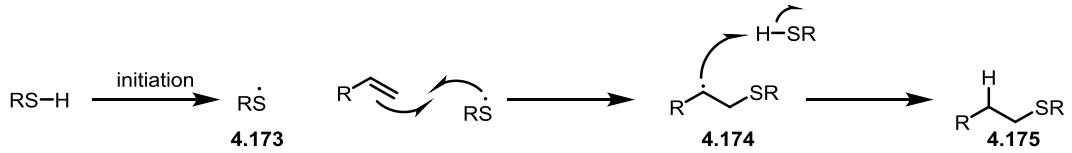
Entry	Temperature	Method	Yield (%)[a]	α:β
1	rt	**A**	53	22:1
2	0 °C	**A**	67	12:1
3	−78 °C	**A**	49	7:1
4	rt	**B**	66	5:1
5	0 °C	**B**	56	18:1
6	−78 °C	**B**	78	11:1
7	−78 °C	**B**	63[b]	10:1 (10:1)[b]

[a] yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard
[b] isolated yield/ratio

Table 4.23. Screening with diphenyl disulfide **4.171**

There is no apparent trend between electrophile addition temperature and method with the yield of sulfide. When diphenyl disulfide **4.171** was added to the benzylic Grignard reagent (method **A**), the reaction became less selective for sulfide *α*-**4.172** as the temperature was decreased, whereas there is no trend in the regioselectivity of the reaction with temperature when the benzylic Grignard reagent was added to diphenyl disulfide **4.171** (method **B**).

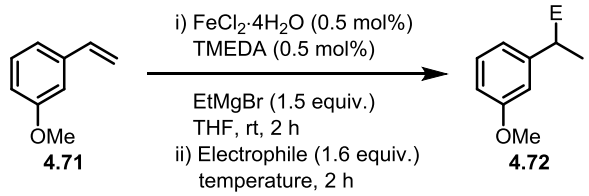
At present, it is difficult to rationalise the difference in reaction regioselectivity with temperature and method and thus the regioselectivity may be dependent on another variable. A possible explanation involves the reaction of residual 3-methoxystyrene **4.71** with diphenyl disulfide **4.171** (*Scheme 4.39*). It is known that alkenes react with thiophenol in a radical-based mechanism to give terminal sulfide **4.175**.[303] Following formation of sulfide radical **4.173** by a radical initiator, such as AIBN or light, addition of the radical to an alkene results in the more stable internal radical intermediate **4.174**, which then abstracts a hydrogen atom to regenerate sulfide radical **4.173** and give terminal sulfide **4.175**. If different amounts of 3-methoxystyrene **4.71** remained in each reaction upon addition of diphenyl disulfide **4.171**, which went on to react together, then different amounts of *β*-sulfide **4.172** would be produced.

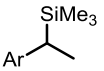
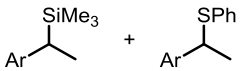


Scheme 4.39. Radical hydrothiolation of alkenes

It is also worth noting that Pivnitsky and co-workers saw a difference in regioselectivity when trapping Grignard reagents prepared by titanium-catalysed hydromagnesiation with different electrophiles (see *Table 4.04*).[242] They proposed that this was due to a difference in reaction rates between Grignard reagent isomerisation and electrophile trapping. Perhaps, in our case, the rate of the reaction between the benzylic Grignard reagent and diphenyl disulfide **4.171** is slow, allowing sufficient time for the Grignard reagent to isomerise.

In order to investigate the regioselectivity of the reaction further, two experiments were performed (*Table 4.24*). In the first, the electrophile trimethylsilyl chloride was added over two hours; it was thought that adding the electrophile slowly might allow sufficient time for the benzylic Grignard reagent to isomerise. Additionally, a 1:1 mixture of trimethylsilyl chloride and diphenyl disulfide (1.6 equivalents of each) was added to the Grignard intermediate to probe the difference in rates of electrophile trapping.



Entry	Temperature	Electrophile	Product[a]
1	rt	Me_3SiCl over 2 h	 α only **4.152**
2	−78 °C	1:1 Me_3SiCl:$(PhS)_2$	 **4.152** 52% + **α-4.172** 49%

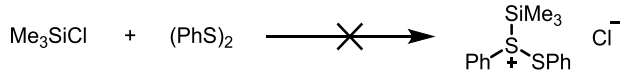
[a] yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard

Table 4.24. Probing the regioselectivity

No insight into the regioselectivity of the reaction was gained through these reactions; the reaction was 100% regioselective for silane **4.152** when trimethylsilyl chloride was added

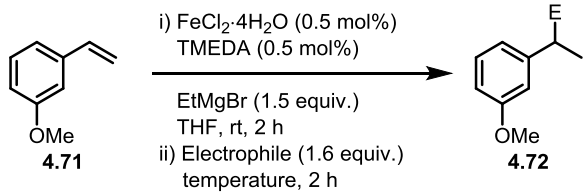
over two hours and a 1:1 mixture of silane **4.152** and *α*-sulfide **4.172** was obtained when a 1:1 mixture of the corresponding electrophiles were added (with negligible formation of *β*-sulfide **4.172**), suggesting that the rate of trapping of each electrophile is similar.

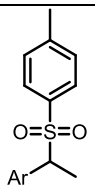
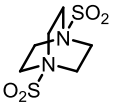
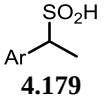
Prior to this, trimethylsilyl chloride and diphenyl disulfide were mixed in order to rule out any competing reaction between the two electrophiles (*Scheme 4.40*); no difference in chemical shift in the ^{1}H NMR spectrum was observed for the trimethyl protons in the mixture compared with pure trimethylsilyl chloride, excluding any competing reaction.



Scheme 4.40. Possible side reaction between the two electrophiles

Two further sulfur electrophiles were explored (*Table 4.25*). The reaction with tosyl chloride **4.176** was poor yielding and product **4.177** was observed in only 8% yield by ^{1}H NMR spectroscopy. Good reactivity was seen with DABSO **4.178** when the benzylic Grignard reagent was added to a 1 M solution of DABSO in THF at −40 °C but sulfinic acid **4.179** proved difficult to isolate, partly due to its extremely high polarity. An acid-base work-up removed the majority of impurities and a second purification by column chromatography on silica gel (using water/*i*-PrOH/EtOAc 1:2:7) gave acid **4.179** in a low 17% yield.



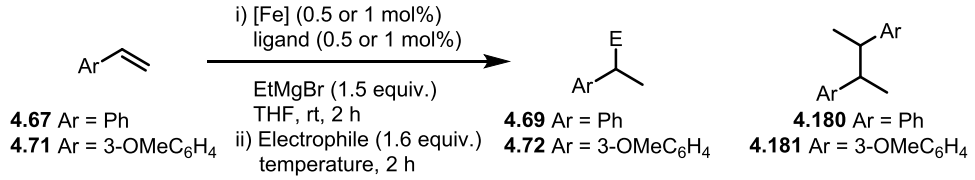
Entry	Temperature	Electrophile	Product[a]	Yield (%)[a]
1	rt	TsCl **4.176**	 **4.177**	8
2	-40 °C	 DABSO **4.178**	 **4.179**	56 (17)[b]

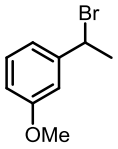
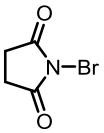
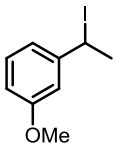
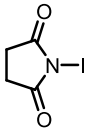
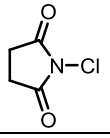
[a] yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard
[b] isolated yield

Table 4.25. Sulfur electrophiles

4.2.4.4 Halogen Electrophiles

The scope of halogen electrophiles was investigated using both the original and second generation catalyst systems (*Table 4.26*).



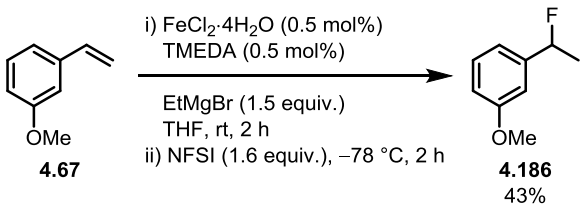
Entry	Catalyst system[a]	Electrophile	Temperature/ °C	Product	Yield(%)[b]
1	$FeCl_2 \cdot 4H_2O$ TMEDA	Br_2	−78	 **4.182**	47
2	$FeCl_2$ BIP	Br_2	rt	 **4.183**	9
3	$FeCl_2$ BIP	Br_2	−78	 **4.183**	57
4	$FeCl_2$ BIP		−78	 **4.183**	38
5	$FeCl_2 \cdot 4H_2O$ TMEDA	I_2	−78	 **4.184**	54
6	$FeCl_2$ BIP	I_2	rt	 **4.185**	23
7	$FeCl_2$ BIP	I_2	−78	 **4.185**	68
8	$FeCl_2$ BIP		−78	6% **4.67** and 13% **4.180**	-
9	$FeCl_2$ BIP		−78	complex mixture	-

[a] $FeCl_2 \cdot 4H_2O$ (0.5 mol%), TMEDA (0.5 mol%) or $FeCl_2$ (1 mol%), BIP (1 mol%)
[b] yield determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard

Table 4.26. Halogen electrophiles

The optimum results for bromination and iodination were 47% and 54% respectively, obtained using elemental bromine and iodine at −78 °C (*Table 4.26*, *entries 1,3,5,7*). At room temperature, lower yields of product and significant amounts of dimer **4.180** were obtained, resulting from oxidative homocoupling of the benzylic Grignard reagent (*entries 2 and 6*). Despite moderate yields by ^{1}H NMR spectroscopy, purification by column chromatography on silica gel proved difficult owing to the apolar nature of the products. It is worth noting that in all cases the transformation is a formal Markovnikov addition of H–X across an alkene and it is possible to achieve higher yields of these products by reacting styrene directly with H–X.[304-305]

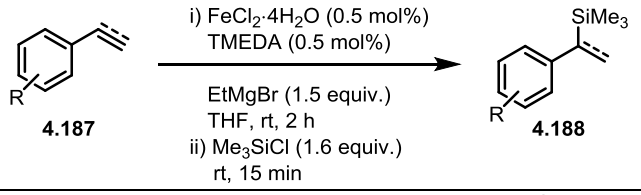
James Paliga investigated the hydrofluorination of styrene **4.67** and following extensive studies into the reaction, fluoride **4.186** was isolated in 43% yield (*Scheme 4.41*).

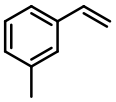
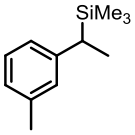
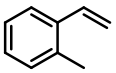
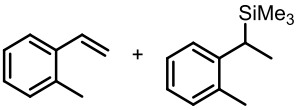
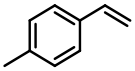
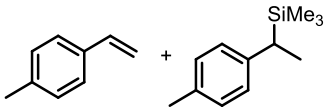
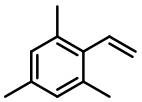
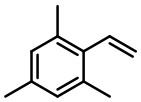
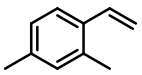
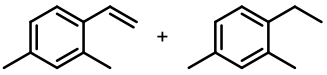
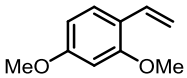
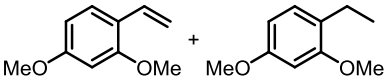


Scheme 4.41. Hydrofluorination of styrene **4.67**

4.2.5 Styrene Scope

After investigating the electrophile scope for the reaction, the styrene scope was explored in order to demonstrate the generality of the procedure. The previous iron-catalysed hydrocarboxylation procedure had been limited to neutral styrene derivatives and those bearing electron-donating substituents[226] and thus it was hoped that the second generation hydrofunctionalisation conditions might be applicable to a wider range of olefins. A variety of styrene derivatives bearing electron-donating substituents were first subjected to the hydromagnesiation conditions and reacted with trimethylsilyl chloride as the model electrophile (*Table 4.27*).



Entry	Olefin	Product[a]
1	 **4.189**	 **4.190** 87%
2	 **4.191**	 **4.191** 58% + **4.192** 17% (65%)[b]
3	 **4.193**	 **4.193** 45% + **4.194** 55% (88%)[b]
4	 **4.195**	 **4.195** quantitative
5	 **4.196**	 **4.196** 65% + **4.197** 30%
6	 **4.198**	 **4.198** 61% + **4.199** 6%

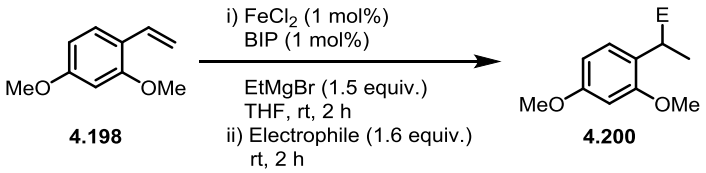
[a] yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard
[b] performed using $FeCl_2$ (1 mol%) and BIP (1 mol%)

Table 4.27. Investigation of electron-rich styrene derivatives

3-Methylstyrene **4.189** was converted to silane in high yield using the hydrofunctionalisation conditions of $FeCl_2 \cdot 4H_2O$ and TMEDA (*Table 4.27, entry 1*). However, for 2- and 4-methylstyrene **4.191** and **4.193**, these conditions gave the corresponding silanes **4.192** and **4.194** in significantly lower yields: 17% and 55% yield respectively (*entries 2 and 3*). Repeating both reactions using the original conditions of $FeCl_2$ and BIP pleasingly restored reactivity and silanes **4.192** and **4.194** were observed in the ^{1}H NMR spectra in 65% and

88% yield respectively. It is interesting that for some substrates a higher yield is obtained using the original conditions than the second generation catalytic system and presumably, BIP is playing a critical role in the reaction (see *section 4.2.2*). 1,3,5-Trimethylstyrene **4.195** was unreactive in the reaction and quantitative starting material was recovered, perhaps as a result of the steric bulk of the aryl group (*entry 4*).

2,4-Dimethylstyrene **4.196** and 2,4-dimethoxystyrene **4.198** gave interesting results (*entries 5 and 6*). Despite ethyl benzene derivatives **4.197** and **4.199** being observed in the ^{1}H NMR spectra, suggesting successful hydromagnesiation, the lack of silane products was puzzling. The reaction with 2,4-dimethoxystyrene **4.198** was repeated with $FeCl_2$ and BIP and the benzylic Grignard intermediate quenched with a range of electrophiles (*Table 4.28*).



Entry	Electrophile	Product[a]
1	Me_3SiCl	**4.198** 19% + **4.199** 81%
2	CO_2	**4.198** 33% + **4.201** 67%
3	**4.101**	**4.198** 29% + **4.202** 70%
4	**4.116**	**4.198** 27% + **4.203** 65%

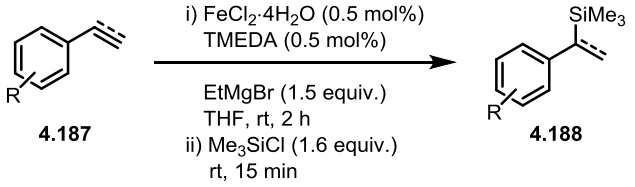
[a] yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard

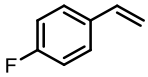
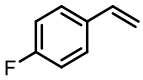
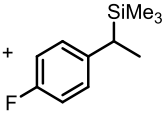
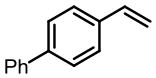
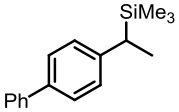
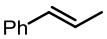
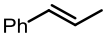
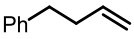
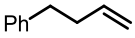
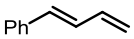
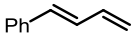
Table 4.28. Reaction of 2,4-dimethoxystyrene **4.198** with electrophiles

In all cases apart from with trimethylsilyl chloride, the corresponding functionalised product

was obtained. This difference cannot be attributed to the trimethylsilyl chloride being "wet", as the reagent was used successfully in subsequent reactions; the reaction outcome must therefore have an electrophile dependence that cannot be explained at present.

A range of styrenes bearing electron-withdrawing substituents, 1,1- and 1,2- disubstituted styrenes, alkyl alkenes, dienes and alkynes were additionally investigated, substrates that were challenging under the original hydrocarboxylation conditions (*Table 4.29*).



Entry	Olefin	Product[a]
1	 **4.204**	 **4.204** 59% (14%)[b] +  **4.205** 19% (38%)[b]
2	 **4.206**	 **4.207** 21%
3	 **4.208**	 **4.208** 72%
4	 **4.209**	 **4.209** 69%
5	 **4.210**	 **4.210** 40%
6	 **4.211**	 **4.211** 95%
7	**3.22**	**3.22** 84%

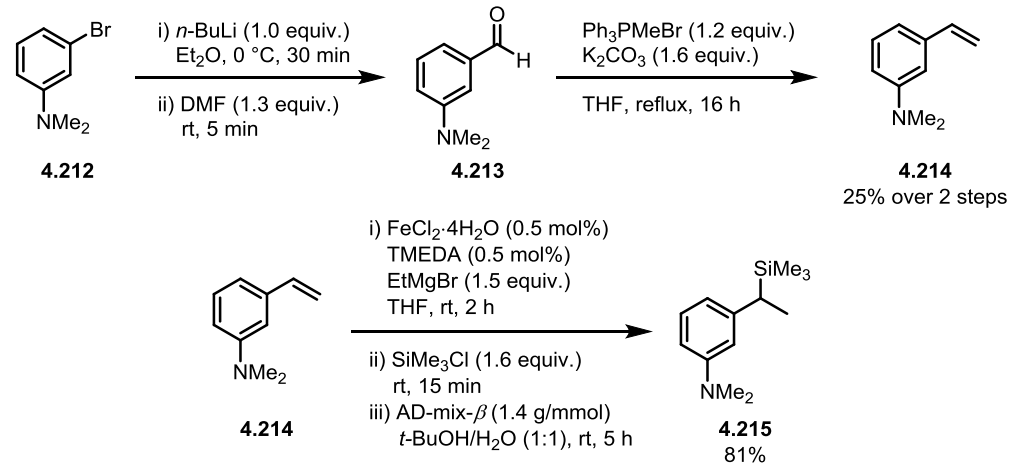
[a] yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard
[b] performed using $FeCl_2$ (1 mol%) and BIP (1 mol%)

Table 4.29. Investigation of challenging olefins

Electron-poor *p*-fluorostyrene **4.204** and *p*-phenylstyrene **4.206** both gave the corresponding silanes in poor yield, with the lack of recovered starting material for *p*-phenylstyrene **4.206**

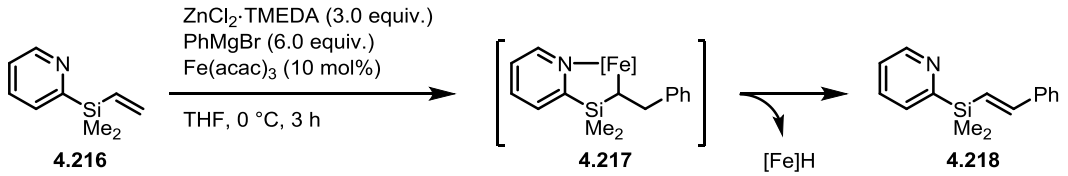
attributed to substrate polymerisation under the reaction conditions (*Table 4.29, entries 1and 2*). However, for *p*-fluorostyrene **4.204**, the yield of the reaction improved from 19% to 38% when the original catalyst system was used. 1,1- and 1,2- disubstituted styrene derivatives **4.208** and **4.209** and alkyl alkene 4-phenyl-1-butene **4.210** were all unreactive (*entries 3-5*). As alkyl alkene **4.210** was unreactive, it was considered that the Grignard intermediate or the transition-state structure for Grignard intermediate formation might require stabilisation *via* conjugation with, or coordination to, another multiple bond, but phenylbutadiene **4.211** did not undergo the reaction (*entry 6*). Finally, alkyne 1-phenyl-1-propyne **3.22** was screened but no reaction occurred (*entry 7*), showing that the second generation hydrofunctionalisation procedure offered no improvement in terms of substrate scope over the original conditions and was currently limited to styrenes.

In addition to the substrates discussed above, a few targeted substrates were synthesised, in the hope that they would undergo hydrofunctionalisation. Owing to the high yields obtained using 3-methoxystyrene **4.71**, 3-dimethylaminostyrene **4.214** was targeted and synthesised in two steps from aniline derivative **4.212** (*Scheme 4.42*). Bromoaniline **4.212** first underwent a lithium-halogen exchange and the anion was subsequently reacted with DMF to give aldehyde **4.213**.[306] Styrene **4.214** was then accessed from aldehyde **4.213** using a Wittig reaction. Under the hydrofunctionalisation conditions, styrene **4.214** was smoothly transformed to silane **4.215**. However, residual styrene made purification of the product by column chromatography difficult owing to the similar retention factors of the two compounds. To aid isolation of silane **4.215**, the mixture was subjected to a dihydroxylation reaction, to convert residual styrene **4.214** into the corresponding diol and thus increase its polarity. Following the successful dihydroxylation reaction, silane **4.215** was isolated in 81% yield.



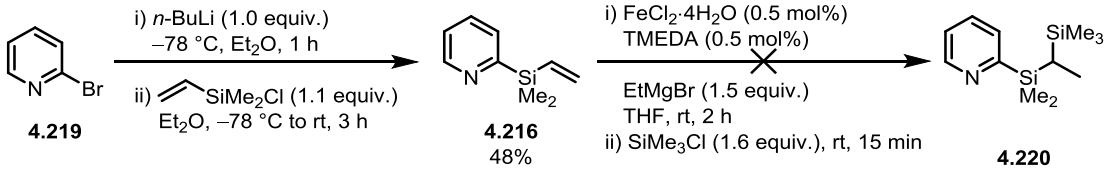
Scheme 4.42. Synthesis and hydrosilylation of 3-dimethylaminostyrene **4.214**

Alkene **4.216** was also targeted, as Nakamura and co-workers have shown that it undergoes a chelation-controlled arylation to form stabilised iron complex **4.217** (*Scheme 4.43*).[307]



Scheme 4.43. Chelation-controlled oxidative arylation of alkene **4.216**

We hoped that vinylsilane **4.216** might react similarly under the hydromagnesiation conditions and thus it was synthesised from 2-bromopyridine **4.219** in 48% yield (*Scheme 4.44*).[308] Unfortunately vinylsilane **4.216** did not react and only starting material was recovered from the attempted hydrofunctionalisation reaction.

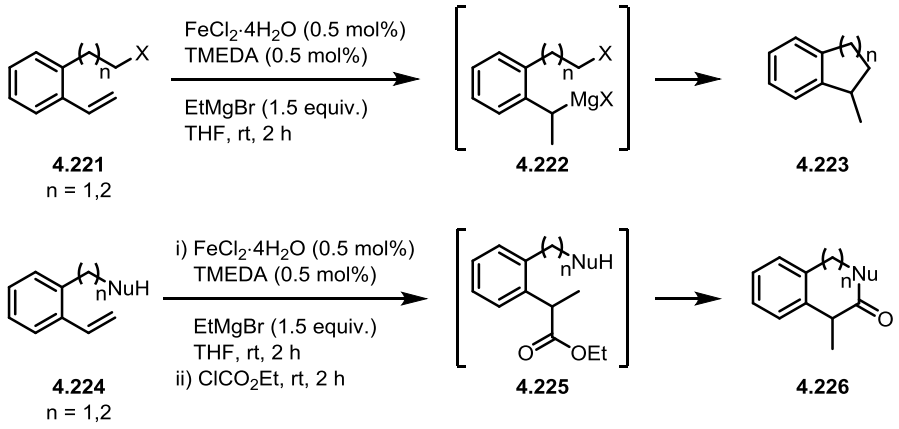


Scheme 4.44. Synthesis and unsuccessful hydrosilylation of vinylsilane **4.216**

4.2.6 Intramolecular Hydrofunctionalisations

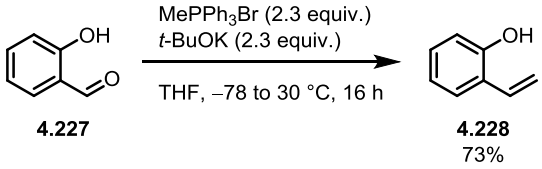
To demonstrate the utility of the hydrofunctionalisation procedure, a series of more complex hydrofunctionalisations were attempted and two strategies were pursued. Firstly, styrene derivatives **4.221** were designed that contained internal electrophiles, in the hope that the benzylic Grignard intermediates **4.222** would react with the electrophile intramolecularly to form benzannulated products **4.223**. Secondly, styrene derivatives **4.224** bearing internal

nucleophiles were investigated, with the intention of reacting benzylic Grignard intermediates **4.225** with a carbonyl electrophile, which could then be attacked intramolecularly by the nucleophile to form complementary benzannulated products **4.226** (*Scheme 4.45*).



Scheme 4.45. Planned intramolecular hydrofunctionalisations

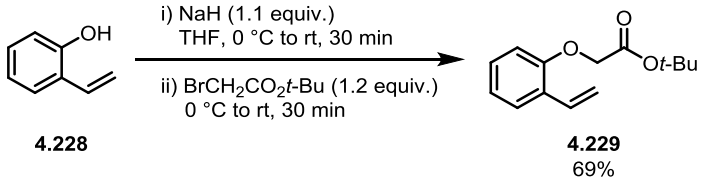
Alcohol **4.228** acted as a common intermediate in the following substrate syntheses and was prepared from aldehyde **4.227** in a high yielding Wittig reaction (*Scheme 4.46*).[309]



Scheme 4.46. Synthesis of alcohol **4.228**

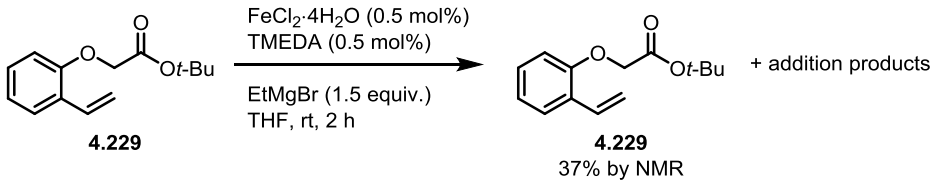
4.2.6.1 Internal Electrophiles

Ester **4.229** was synthesised from alcohol **4.228** using a simple S_N2 reaction (*Scheme 4.47*).



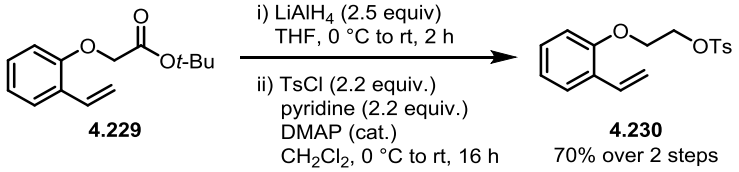
Scheme 4.47. Synthesis of ester **4.229**

When ester **4.229** was subjected to the hydrofunctionalisation conditions, 37% starting material by ^{1}H NMR spectroscopy was recovered alongside a complex mixture of products, presumably resulting from addition of ethylmagnesium bromide to the ester functionality (*Scheme 4.48*).



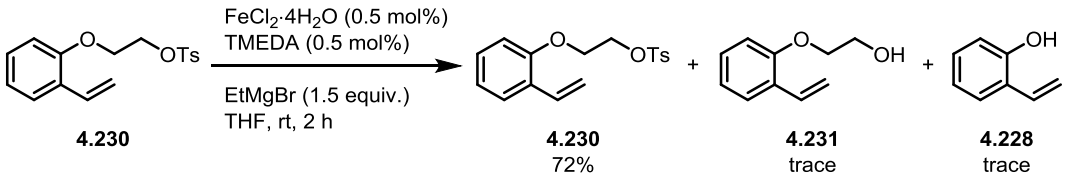
Scheme 4.48. Unsuccessful electrophile trapping with ester **4.229**

Given that a carbonyl functionality was susceptible to nucleophilic attack by a Grignard reagent, it was hoped that a halide or halide equivalent would be less susceptible. To this end, tosylate **4.230** was synthesised in two steps, by reducing unsuccessful ester **4.229** to the alcohol, followed by a tosylate protection (*Scheme 4.49*).



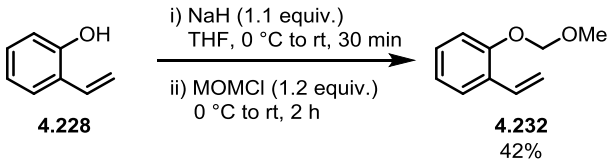
Scheme 4.49. Synthesis of tosylate **4.230**

Tosylate **4.230** was subjected to the hydrofunctionalisation conditions but although two additional spots were present on the TLC plate upon analysis, these were subsequently identified as the deprotected alcohols **4.231** and **4.228** (*Scheme 4.50*).



Scheme 4.50. Unsuccessful substitution with tosylate **4.230**

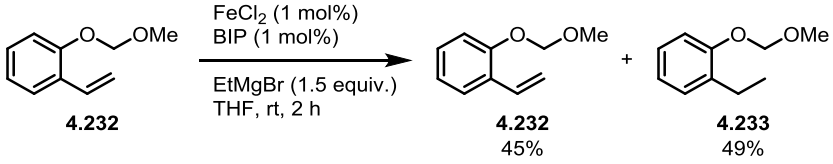
As benzopyran formation proved unsuccessful, benzofuran formation was attempted next using methoxymethyl (MOM)-protected alcohol **4.232**. Alcohol **4.228** was protected using MOM chloride to obtain ether **4.232** in 42% yield (*Scheme 4.51*).



Scheme 4.51. Synthesis of MOM-protected alcohol **4.232**

MOM-protected alcohol **4.232** underwent successful hydromagnesiation using $FeCl_2$ and BIP (these conditions were used, as superior yields had been achieved with them for challenging substrates) and whilst 45% of starting material was recovered, 49% of

ethylbenzene derivative **4.233** resulted. The lack of benzofuran product suggested that either methoxide was not a suitable leaving group or that cyclisation was unfavourable, although 5-exo-tet cyclisations are allowed by Baldwin's rules.[310-311]

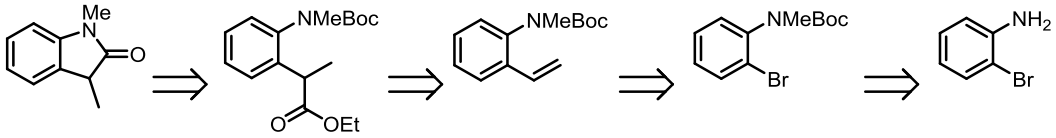


Scheme 4.52. Unsuccessful substitution with methyl ether **4.232**

4.2.6.2 Internal Nucleophiles

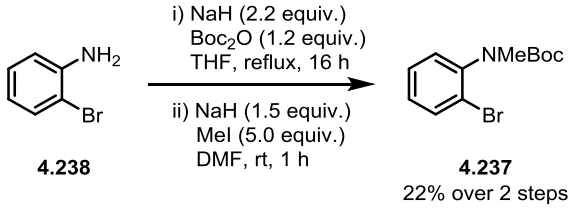
For those styrene derivatives containing internal nucleophiles, the nucleophile was protected prior to hydromagnesiation to prevent competing deprotonation of the nucleophile (OH, NH) by ethylmagnesium bromide. It was hoped that deprotection of the nucleophile upon work-up or in a subsequent step would facilitate a rapid intramolecular cyclisation.

Nitrogen-containing styrene **4.236** was designed in which the nitrogen was protected with a methyl and Boc group (*Scheme 4.53*). Performing the hydromagnesiation and trapping the benzylic Grignard reagent with ethyl chloroformate would give **4.235**, which after removal of the Boc group, would hopefully cyclise to form 2-oxindole derivative **4.234**.



Scheme 4.53. Retrosynthetic analysis of nitrogen-containing styrene **4.236**

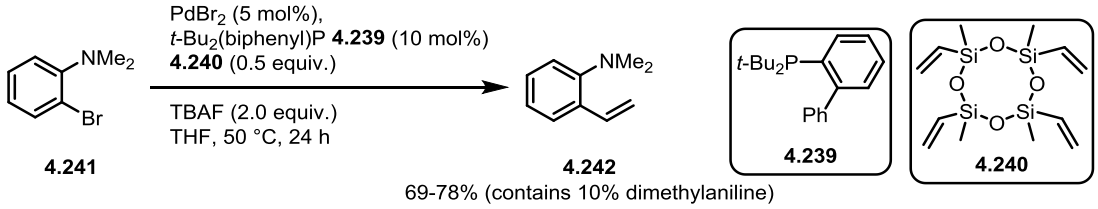
Styrene **4.236** was targeted from 2-bromoaniline **4.238** using a protection and cross-coupling strategy. Aniline **4.238** was first protected with a Boc group followed by methylation (*Scheme 4.54*).[312]



Scheme 4.54. Boc and methyl protection of 2-bromoaniline **4.238**

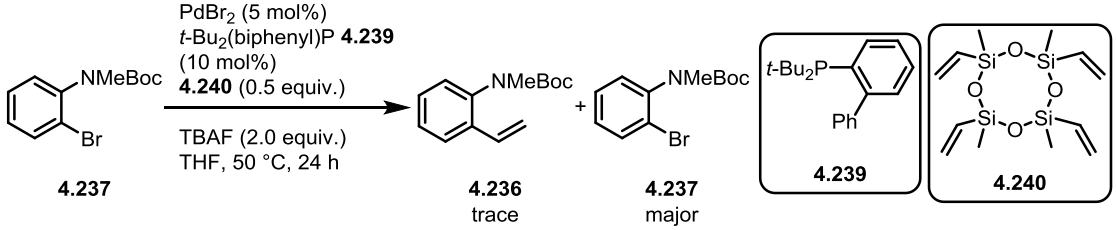
With nitrogen-protected bromide **4.237** in hand, we began to consider the cross-coupling

conditions required for the installation of the vinyl group. After conducting a literature search, the most relevant conditions found for the transformation were developed by Denmark and Butler and used polyvinylsiloxane **4.240** as the vinyl source (*Scheme 4.55*).[313]



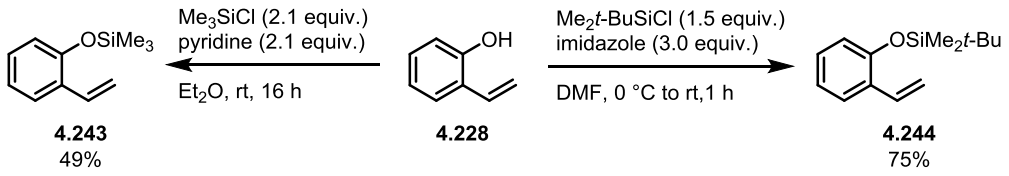
Scheme 4.55. Cross-coupling conditions

Although long reaction times were required for the vinylation of bromides bearing electron-donating substituents, the yields were unaffected. However, for the substrate of interest, **4.241**, the product **4.242** was accompanied by 10% of inseparable reduction product dimethylaniline. When substrate **4.237** was subjected to these conditions, although a trace of the intended product was visible in the ^{1}H NMR of the crude reaction mixture, recovered starting material was the major component (*Scheme 4.56*).



Scheme 4.56. Attempted cross-coupling

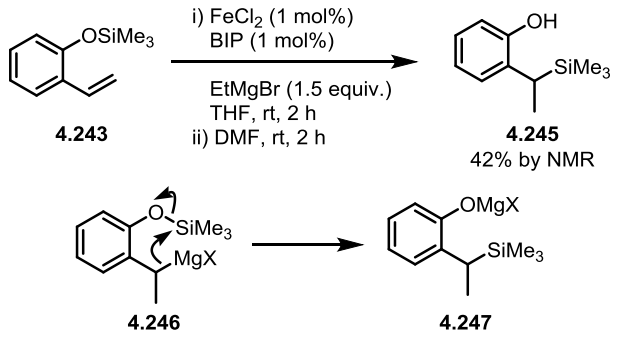
Opting to explore oxygen nucleophiles rather than focus on alternative cross-coupling conditions, styrenes **4.243** and **4.244** were targeted, which were both synthesised from alcohol **4.228** and the corresponding silyl chlorides (*Scheme 4.57*).[314-315] TMS-protected alcohol **4.243** is less sterically hindered than TBS-protected alcohol **4.244** and thus hydromagnesiation may be more efficient and higher yielding, but more labile.



Scheme 4.57. Synthesis of silyl-protected alcohols **4.243** and **4.244**

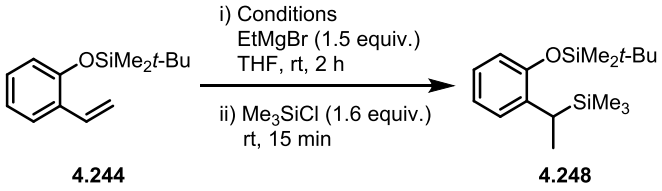
TMS-protected alcohol **4.243** was first subjected to the hydrofunctionalisation conditions

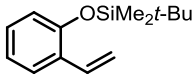
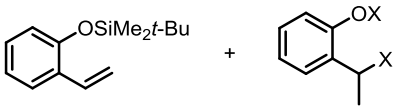
using the more reactive original conditions of $FeCl_2$ and BIP, and DMF as the electrophile in the hope of forming a lactol (*Scheme 4.58*). However, silane **4.245** was isolated as the major product of the reaction, which presumably arises from a successful hydromagnesiation, followed by an intramolecular silyl migration. This unexpected rearrangement was hoped to be less likely with TBS-protected alcohol **4.244**.



Scheme 4.58. Hydrofunctionalisation of TMS-protected alcohol **4.243** and silyl migration

To initially assess the extent of hydromagnesiation for TBS-protected alcohol **4.244**, trimethylsilyl chloride was used as the model electrophile (*Table 4.30*).



Entry	Conditions	Product[a]
1	$FeCl_2 \cdot 4H_2O$ (0.5 mol%) TMEDA (0.5 mol%)	 **4.244** 92%
2	$FeCl_2$ (1 mol%) BIP (1 mol%)	 **4.244** 74% + **4.249** X = $SiMe_2t$-Bu, $SiMe_3$ or H 12%

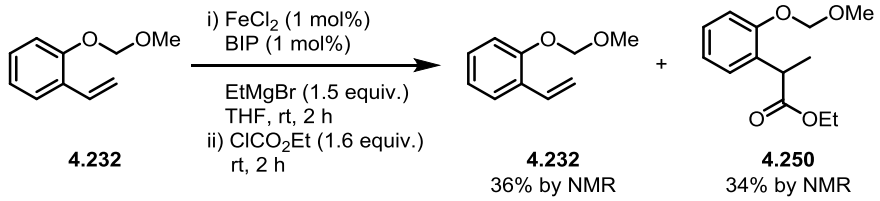
[a] yield determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard

Table 4.30. Attempted hydrofunctionalisation with TBS-protected alcohol **4.244**

Using the simpler conditions of $FeCl_2 \cdot 4H_2O$ and TMEDA, no reaction occurred and only starting material was recovered. With the original conditions of $FeCl_2$ and BIP, 74% of starting material was recovered alongside 12% of a product resulting from

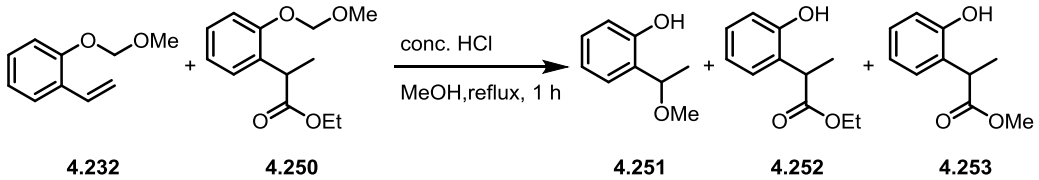
hydromagnesiation. Owing to the number of overlapping silyl peaks in the ^{1}H NMR spectrum of the crude reaction mixture, it was difficult to identify the exact product but since the extent of hydromagnesiation was low, this substrate was not pursued.

As MOM-protected alcohol **4.232** had proven unsuccessful as part of the internal electrophile strategy, it was hoped that the alcohol functionality in the same substrate could act as an internal nucleophile following methyl ether cleavage. With this in mind, ether **4.232** was subjected to hydromagnesiation and reaction with ethyl chloroformate (*Scheme 4.59*). 34% yield of product **4.250** by ^{1}H NMR spectroscopy was observed, alongside 36% recovered starting material **4.232**.



Scheme 4.59. Successful hydromagnesiation and trapping with ethyl chloroformate

To test the feasibility of the deprotection and subsequent cyclisation to a lactone the crude reaction mixture was subjected to deprotection conditions (*Scheme 4.60*). No lactone product was observed but instead a mixture of products resulting from deprotection (**4.252**), transesterification (**4.253**) and acid-catalysed addition of methanol across unreacted styrene (**4.251**). Even though hydroxy esters **4.252** and **4.253** were present in the reaction, no cyclisation occurred and hence benzannulation was not pursued further.



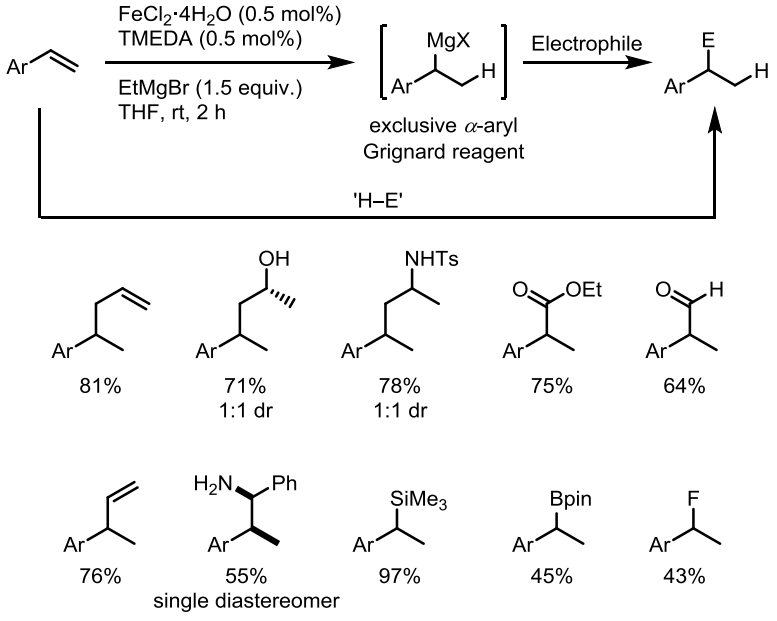
Scheme 4.60. Methyl ether deprotection of crude reaction mixture

Despite two complementary cyclisation strategies investigated and a number of different substrates synthesised and explored, no successful cyclisation occurred.

4.3 Conclusions

In conclusion, a highly operationally simple procedure for the hydrofunctionalisation of styrene derivatives was developed that uses simpler reagents and is more robust than the original conditions used for the hydrocarboxylation of styrene derivatives.[226] The new procedure uses a bench-stable iron hydrate precatalyst and the ligand, TMEDA, is commercially available and can be used as purchased. Even "wet" THF can be used for the hydrofunctionalisation—THF straight from a bottle that has been open to the atmosphere. The hydrofunctionalisation procedure is also highly efficient, using a catalyst loading of just 0.5 mol%.

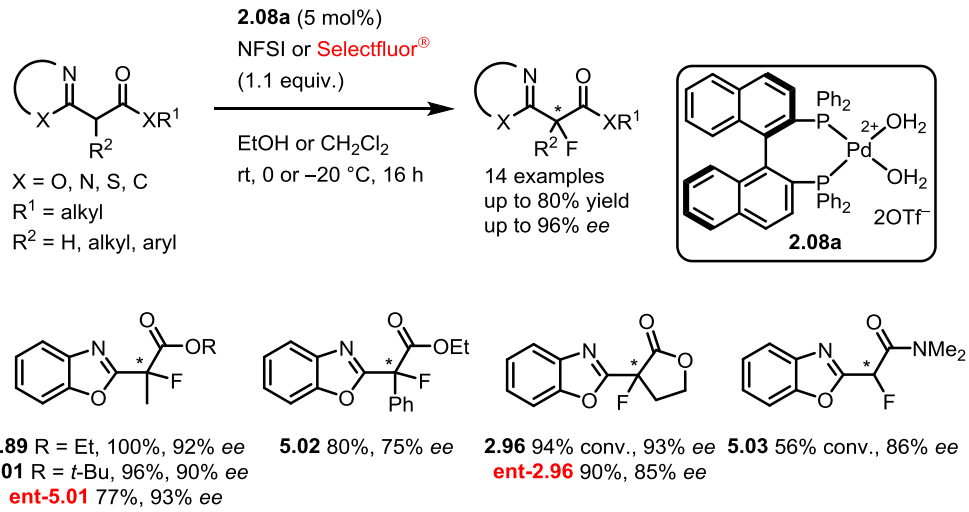
With this second generation catalyst system a range of carbon–carbon and carbon–heteroatom bonds, including the products of formal cross-coupling reactions, hydrosilylation and hydroboration, were constructed, highlighting the versatility and applicability of this system (*Scheme 4.61*). Using a common benzylic Grignard reagent, all the hydrofunctionalisation reactions were highly regioselective for the α-functionalised product and the electrophile trapping was demonstrated to be both chemo- and regioselective.



Scheme 4.61. Hydrofunctionalisation of styrene derivatives and selected products

Chapter 5. General Conclusions and Future Work

Over the course of this endeavour, three types of reaction were successfully developed and the substrate scope of each explored. Palladium catalysis was used for the enantioselective fluorination of a series of azaarylacetates and amides and for the C–H functionalisation of a range of ferrocene derivatives, with both reactions utilising a different property of palladium. The enantioselective fluorination of azaarylacetates and amides focussed on the use of palladium as a Lewis acid and its ability to form a chiral complex with a range of enantiopure ligands. Whilst the reaction proved highly stereoselective only with benzoxazoles, a variety of 2-fluorobenzoxazolyl acetates and amides were prepared in excellent *ee* (*Scheme 5.01*). Both enantiomeric products were obtained from a single catalytic system by switching the fluorinating agent from NFSI to Selectfluor®.



Scheme 5.01. Palladium-catalysed enantioselective fluorination of benzoxazolyl acetates and amides

The successful reaction of benzoxazoles was postulated to be a result of the unique binding of these substrates with the palladium catalyst, with them binding through oxygen and not through nitrogen as would perhaps be expected (*Figure 5.01*). Future work in this area would be the development of a general catalyst system that is applicable to a range of azaarylacetates and amides, which might involve the exploration of organocatalysis and/or phase-transfer catalysis.

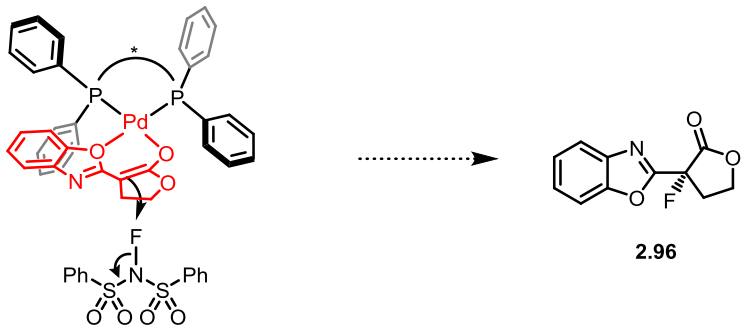
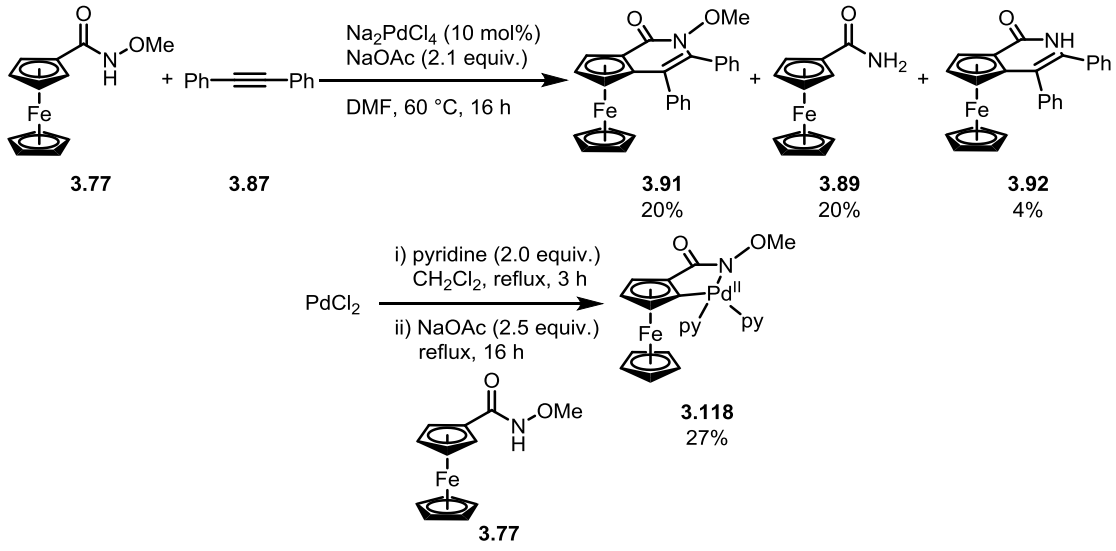


Figure 5.01. Possible transition-state structure for fluorination of benzoxazolyl acetates and amides

Secondly, the C–H functionalisation of ferrocene derivatives was investigated, which relied on a series of two-electron redox processes for palladium (*Scheme 5.02*). Although the reaction proved challenging to optimise, the reaction was nevertheless successful and allowed the preparation of a novel structural motif (e.g. **3.91** and **3.92**). Palladacycle **3.118** was also synthesised as a potential reaction intermediate but unfortunately no further mechanistic insight could be gained through its use.

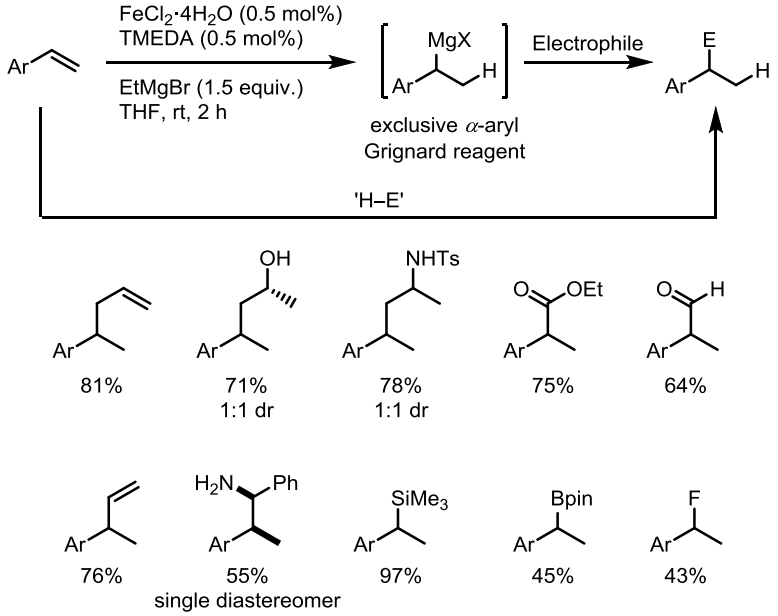


Scheme 5.02. Oxidative annulation of ferrocenecarboxamide **3.77** and synthesis of palladacycle **3.118**

After the completion of this project, the high yielding oxidative annulation of ferrocenearylcarboxamides was reported, which was facilitated through the precise choice of reaction conditions.[225] An obvious future endeavour would be to render this reaction enantioselective.

The focus of this thesis then changed and iron catalysis was explored, as this sustainable and environmentally benign metal is rapidly becoming a viable alternative for reactions that have

been traditionally catalysed by precious metals. To this end the broad operationally simple hydrofunctionalisation of alkenes was developed, based on work previously developed in the Thomas group.[226] This reaction relied on the ability of Grignard reagents to reduce an inexpensive bench-stable iron precatalyst to an active low-valent iron catalyst. Using this procedure, a range of functionalised products were synthesised including the products of formal cross-coupling reactions, hydrosilylation and hydroboration (*Scheme 5.03*).



Scheme 5.03. Iron-catalysed hydrofunctionalisation of styrenes

The reaction was limited to styrenes and thus future work would concentrate on the extension of this reaction to alkyl alkenes and alkynes. The investigation of alternative methods to activate the iron precatalyst would also be beneficial, as the current reaction relies on Grignard reagents that are moisture and air sensitive. Research into an enantioselective variant of this reaction would also be a worthwhile pursuit.

Chapter 6. Experimental

6.1 Experimental Methods

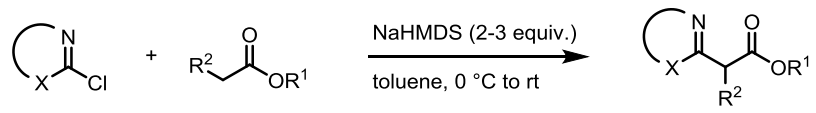
CH_2Cl_2, Et_2O, MeCN, MeOH, THF and toluene were dried and purified by passage through activated alumina columns using a solvent purification system. All commercially available reagents were used as received. Aqueous sulphate buffer was prepared by dissolving Na_2SO_4 (1.5 mol) and H_2SO_4 (0.5 mol) in water and adding water to give a total volume of 2000 cm^3. Thin phase chromatography (TLC) was performed on Merck DF-Alufoilien $60F_{254}$ 0.2 mm precoated plates. Product spots were visualized by UV light at 254 nm, and subsequently developed using vanillin or potassium permanganate solution as appropriate. Flash column chromatography was carried out using silica gel (Fisher Scientific 60Å particle size 35-70 micron) employing step gradient elution in the mobile phase stated. Pet. ether refers to petroleum ether 40-60. Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Infra-red spectra were recorded on Shimadzu IRAffinity-1 spectrometer (serial no. A213749) as a dilute solution in $CDCl_3$. ^1H NMR spectra were recorded on a Bruker Avance (400 and 600 MHz), a Bruker Avance III (400 and 500 MHz) or a Bruker Avance III HD (500 and 600 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using residual protonated solvent as internal standard ($CDCl_3$ at 7.27 ppm, CD_3CN at 1.94 ppm, $(CD_3)_2SO$ at 2.50 ppm, $(CD_3)_2CO$ at 2.05 ppm, CD_3OD at 3.31 ppm). Abbreviations used in the description of resonances are: br (broad), s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sext (sextet). Coupling constants (*J*) are quoted to the nearest 0.5 Hz. Proton-decoupled ^{13}C NMR spectra were recorded on a Bruker Avance III (100.6 and 125.8 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using deuterated solvent as internal standard ($CDCl_3$ at 77.0 ppm, CD_3CN at 1.32 ppm, $(CD_3)_2SO$ at 39.5 ppm, $(CD_3)_2CO$ at 29.8 ppm, CD_3OD at 49.00 ppm). Assignments were made using the DEPT (distortionless enhancement by polarisation transfer) sequence with

secondary pulses at 90° and 135°. Proton-decoupled ^{19}F NMR spectra were recorded on a Bruker Avance III (376 MHz) or a Bruker Avance III HD (471 MHz) spectrometer. Chemical shifts are reported in parts per million (ppm) downfield of $CFCl_3$, using fluorobenzene as internal standard (C_6H_5F at −113.2 ppm). High resolution mass spectra were recorded on a Finnigan MAT 900 XLT or a Finnigan MAT 95XP spectrometer at the EPSRC National Mass Spectrometry Service Centre, University of Wales, Swansea, or on a Finnigan MAT 900 XLT (EI) or a Bruker Micro TOF focus II (ESI) spectrometer at the School of Chemistry, University of Edinburgh. Optical rotations were performed on an Optical Activity POLAAR 20 polarimeter with a path length of 1 dm. Concentrations are quoted in g/100 mL, specific rotations are quoted in 10^{-1} deg m^2 g^{-1}. Chiral HPLC analysis was performed on an Agilent 1100 instrument using 4.6 x 250 mm columns. Authentic racemic samples of products for chiral HPLC assay determinations were obtained using $Ni(ClO_4)_2$- or $Ni(OAc)_2$/2,2'-bipyridyl as the catalyst in EtOH or CH_2Cl_2.

6.2 Enantioselective Fluorination of Azaarylacetates and Amides

6.2.1 General Procedures

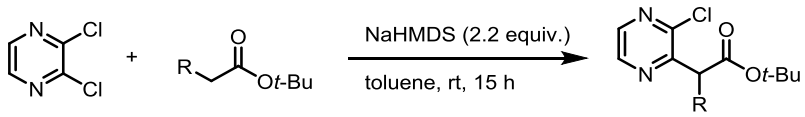
General Procedure A: Preparation of Azaarylacetates 2.58[126]



2.56 **2.57** **2.58**

To a stirred solution of heterocyclic chloride **2.56** (1 equiv.) and ester **2.57** (1-3 equiv.) in toluene (0.2 M) at 0 °C was added NaHMDS (0.6 M in toluene, 2-3 equiv.). The reaction was warmed to room temperature and stirred until completion by TLC analysis. The reaction was quenched with an equal volume of sat. aq. NH_4Cl, the phases separated, and the aqueous phase extracted with EtOAc. The combined organics were dried ($MgSO_4$) and the solvent removed *in vacuo*. The product **2.58** was purified by flash chromatography.

General Procedure B : Preparation of Pyrazinylacetates[316]

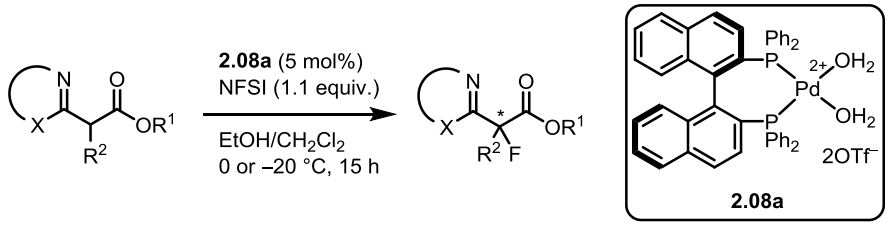


To a stirred solution of 2,3-dichloropyrazine (1 equiv.) in toluene (0.2 M) was added NaHMDS (0.6 M in toluene, 2.2 equiv.). To the mixture was added ester (1.1 equiv.) dropwise and the reaction stirred at room temperature for 16 h. The reaction was quenched with an equal volume of sat. aq. NH_4Cl, the phases separated, and the aqueous phase extracted with EtOAc. The combined organics were dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash chromatography.

General Procedure C: Preparation of Thiadiazolylacetates

To a stirred solution of chloride **2.81** (1 equiv.) in THF (0.1 M) under nitrogen was added LiHMDS (1.0 M in THF, 2.3 equiv.). To the mixture was added the appropriate alkyl propionate (1.1 equiv.) and the reaction heated to 60 °C. The mixture was stirred for 30 min, cooled to room temperature, and quenched with an equal volume of 1 N aq. HCl. The phases were separated, the aqueous phase extracted with Et_2O and the combined organics dried ($MgSO_4$). The solvent was removed *in vacuo* and the product purified by column chromatography.

General Procedure D: Enantioselective Fluorination of Azaarylacetates

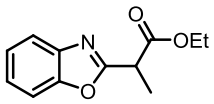


To a stirred solution of azaarylacetate or amide (1 equiv.) in EtOH (acyclic esters and amides) or CH_2Cl_2 (cyclic esters and amides) (0.2 M) at room temperature, 0 °C or −20 °C

was added [((*R*)-BINAP)Pd$(OH_2)_2$]$^{2+}$2OTf$^-$ **2.08a** (5 mol%). The mixture was stirred for 10 min and NFSI (1.1 equiv.) added. The reaction was stirred for 15 h and quenched with an equal volume of sat. aq. KI. The phases were separated and the aqueous phase extracted with EtOAc. The combined organics were washed with sat. aq. $Na_2S_2O_3$, dried ($MgSO_4$), and the solvent removed *in vacuo*. The product was purified by flash chromatography.

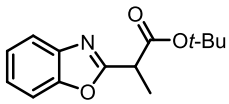
6.2.2 Data

Ethyl 2-(1,3-benzoxazol-2-yl)propanoate 2.59



General procedure A was applied to 2-chlorobenzoxazole (740 μL, 6.51 mmol), ethyl propionate (2.24 mL, 19.5 mmol) and NaHMDS (0.6 M in toluene, 32.5 mL, 19.5 mmol). The reaction was stirred for 2 h and purified by flash chromatography (*n*-hexane/EtOAc 19:1→2:1) to give *azaarylacetate* **2.59** (910 mg, 64%) as a yellow oil. R_f 0.38 (*n*-hexane/EtOAc 9:1); IR (film, cm^{-1}) 2988, 2926, 2854, 1743 (C=O), 1614, 1572, 1456, 1266, 1243; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74-7.71 (1H, m, Ar**H**), 7.53-7.51 (1H, m, Ar**H**), 7.35-7.33 (2H, m, Ar**H**), 4.38 (1H, dq, *J* = 11.0, 7.0 Hz, C**H**$_a$CH$_b$CH$_3$), 4.33 (1H, dq, *J* = 11.0, 7.0 Hz, CH$_a$C**H**$_b$CH$_3$), 4.13 (1H, q, *J* = 7.5 Hz, C**H**CH$_3$), 1.74 (3H, d, *J* = 7.5 Hz, CHC**H**$_3$), 1.26 (3H, t, *J* = 7.0 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 170.3 (C), 164.0 (C), 150.9 (C), 141.0 (C), 125.0 (CH), 124.3 (CH), 120.1 (CH), 110.6 (CH), 61.8 (CH_2), 40.6 (CH), 15.0 (CH_3), 14.0 (CH_3); HRMS (ES) Exact mass calcd for $C_{12}H_{14}NO_3$ $[M+H]^+$: 220.0968, found: 220.0968.

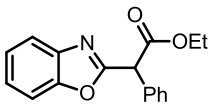
***tert*-Butyl 2-(1,3-benzoxazol-2-yl)propanoate 2.60**



General procedure A was applied to 2-chlorobenzoxazole (70 μL, 0.65 mmol), *tert*-butyl propionate (0.19 mL, 2.0 mmol) and NaHMDS (0.6 M in toluene, 3.25 mL, 1.95 mmol). The reaction was stirred for 2 h and purified by flash chromatography (*n*-hexane/Et_2O 19:1→9:1) to give *azaarylacetate* **2.60** (120 mg, 73%) as a colourless solid. R_f 0.37 (*n*-hexane/EtOAc 9:1); m.p. 32 °C; IR (film, cm^{-1}) 2983, 2942,

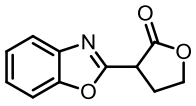
1738 (C=O), 1615, 1573, 1456, 1370, 1243, 1152; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71-7.67 (1H, m, Ar**H**), 7.50-7.46 (1H, m, Ar**H**), 7.30-7.26 (2H, m, Ar**H**), 4.02 (1H, q, *J* = 7.5 Hz, C**H**CH_3), 1.67 (3H, d, *J* = 7.5 Hz, CHC**H**$_3$), 1.41 (9H, s, C(C**H**$_3$)$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 169.3 (C), 164.4 (C), 150.7 (C), 140.9 (C), 124.7 (CH), 124.1 (CH), 119.8 (CH), 110.3 (CH), 82.0 (C), 41.4 (CH), 28.7 (3 x CH_3), 14.8 (CH_3); HRMS (ES) Exact mass calcd for $C_{14}H_{18}NO_3$ $[M+H]^+$: 248.1281, found: 245.1285.

Ethyl 2-(1,3-benzoxazol-2-yl)-2-phenylacetate 2.61



General procedure A was applied to 2-chlorobenzoxazole (70 μL, 0.65 mmol), ethyl phenylacetate (0.19 mL, 2.0 mmol) and NaHMDS (0.6 M in toluene, 3.25 mL, 1.95 mmol). The reaction was stirred for 2 h and purified by flash chromatography (pet. ether/Et_2O 4:1→3:1) to give *azaarylacetate* **2.61** (175 mg, 91%) as a colourless oil. R_f 0.56 (pet. ether/EtOAc 4:1); IR (film, cm^{-1}) 1738 (C=O), 1612, 1566, 1497, 1454, 1368, 1300, 1269, 1240, 1193; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78-7.74 (1H, m, Ar**H**), 7.59-7.55 (2H, m, Ar**H**), 7.54-7.49 (1H, m, Ar**H**), 7.45-7.35 (3H, m, Ar**H**), 7.35-7.31 (2H, m, Ar**H**), 5.37 (1H, s, C**H**Ph), 4.35-4.23 (2H, m, C**H**$_2$$CH_3$), 1.27 (3H, t, *J* = 7.0 Hz, CH_2C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 168.4 (C), 162.2 (C), 151.0 (C), 140.9 (C), 133.4 (C), 129.0 (2 x CH), 128.8 (2 x CH), 128.3 (CH), 125.1 (CH), 124.3 (CH), 120.2 (CH), 110.6 (CH), 62.1 (CH), 52.2 (CH_2), 13.9 (CH_3); HRMS (ES) Exact mass calcd for $C_{17}H_{16}NO_3$ $[M+H]^+$: 282.1125, found: 282.1127.

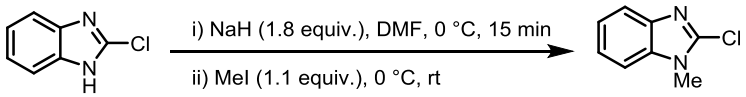
3-(1,3-Benzoxazol-2-yl)oxolan-2-one 2.62[317]



General procedure A was applied to 2-chlorobenzoxazole (740 μL, 6.5 mmol), γ-butyrolactone (500 μL, 6.51 mmol) and NaHMDS (0.6 M in toluene, 13.0 mL, 7.81 mmol). The reaction was stirred for 6 h and purified by flash chromatography (pet. ether/EtOAc 4:1→2:1). The residue was co-evaporated using xylenes (5 x 5mL) to remove remaining γ-butyrolactone to give azaarylacetate **2.62** (524 mg, 40%)

as a cream solid. R_f 0.56 (pet. ether/EtOAc 1:1); m.p. 72 °C (lit. 76-80 °C)[317]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75-7.70 (1H, m, Ar**H**), 7.59-7.52 (1H, m, Ar**H**), 7.40-7.33 (2H, m, Ar**H**), 4.67 (1H, ddd, *J* = 9.0, 8.5, 4.5 Hz, $CO_2C\mathbf{H}_aH_bCH_2CH$), 4.48 (1H, ddd, *J* = 9.0, 8.0, 7.5 Hz, $CO_2CH_a\mathbf{H}_bCH_2CH$), 4.23 (1H, t, *J* = 9.0 Hz, $CO_2CH_2CH_2C\mathbf{H}$), 2.99 (1H, dq, *J* = 13.0, 8.5 Hz, $CO_2CH_2C\mathbf{H}_aH_bCH$), 2.80 (1H, dddd, *J* = 13.0, 9.0, 7.0, 4.5 Hz, $CO_2CH_2CH_a\mathbf{H}_bCH$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 172.4 (C), 160.7 (C), 151.1 (C), 140.8 (C), 125.5 (CH), 124.7 (CH), 120.1 (CH), 110.8 (CH), 67.3 (CH_2) 40.6 (CH_2), 27.8 (CH). Data consistent with literature.[318]

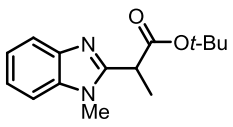
2-Chloro-1-methyl-1*H*-1,3-benzodiazole 6.01[319]



82%

To 2-chlorobenzimidiazole (1.50 g, 9.83 mmol) in *N*,*N*-dimethylformamide (15 mL) at 0 °C under nitrogen was added sodium hydride (60% in mineral oil, 708 mg, 17.7 mmol) portionwise. The reaction was stirred for 15 min and methyl iodide (0.64 mL, 10.3 mmol) added. The reaction was stirred for a further 15 min and quenched by pouring the mixture onto water (100 mL). The resultant white solid was collected by filtration and dried *in vacuo* to give benzodiazole **6.01** (1.35 g, 82%) as a white solid. R_f 0.60 (pet. ether/EtOAc 2:1); m.p. 106-108 °C (lit. 113-114 °C)[318]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75-7.71 (1H, m, Ar**H**), 7.36-7.29 (3H, m, Ar**H**), 3.81 (3H, s, $NC\mathbf{H}_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 141.6 (C), 140.9 (C), 135.6 (C), 123.1 (CH), 122.6 (CH), 119.4 (CH), 109.2 (CH), 30.5 (CH_3). Data consistent with literature.[320]

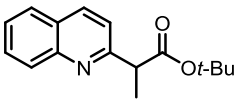
***tert*-Butyl 2-(1-methyl-1*H*-1,3-benzodiazol-2-yl)propanoate 2.63**



General procedure A was applied to **6.01** (500 mg, 3.00 mmol), *tert*-butyl propionate (1.35 mL, 9.00 mmol) and NaHMDS (0.6 M in toluene, 15.0 mL, 9.00 mmol). The reaction was stirred for 16 h and purified by flash

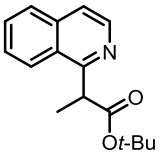
chromatography (pet. ether/EtOAc 9:1→2:1) to give *azaarylacetate* **2.63** as a colourless solid (52%, 62% brsm). R_f 0.58 (pet. ether/EtOAc 1:1); m.p. 122 °C; IR (film, cm^{-1}) 2978, 2938, 1732 (C=O), 1504, 1470, 1395, 1369, 1277, 1236, 1153; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (1H, d, *J* = 7.5 Hz, Ar**H**), 7.35-7.24 (3H, m, Ar**H**), 4.04 (1H, q, *J* = 7.0 Hz, C**H**CH_3), 3.78 (3H, s, NC**H**$_3$), 1.76 (3H, d, *J* = 7.0 Hz, CHC**H**$_3$), 1.43 (9H, s, C(C**H**$_3$)$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 170.4 (C), 152.7 (C), 142.1 (C), 135.9 (C), 122.5 (CH), 122.0 (CH), 119.7 (CH), 109.1 (CH), 82.0 (C), 39.9 (CH), 30.0 (CH_3), 27.9 (3 x CH_3), 15.3 (CH_3); HRMS (ES) Exact mass calcd for $C_{15}H_{21}N_2O_2$ $[M+H]^+$: 261.1598, found: 261.1595.

***tert*-Butyl 2-(quinolin-2-yl)propanoate 2.64**



General procedure A was applied to 2-chloroquinoline (500 mg, 3.06 mmol), *tert*-butyl propionate (1.38 mL, 9.17 mmol) and NaHMDS (0.6 M in toluene, 15.3 mL, 9.17 mmol). The reaction was stirred for 6 h and purified by flash chromatography (pet. ether/Et_2O 19:1→7:1) to give *azaarylacetate* **2.64** (192 mg, 24%) as a yellow oil. R_f 0.51 (pet. ether/EtOAc 9:1); IR (film, cm^{-1}) 2978, 2936, 1728 (C=O), 1618, 1601, 1458, 1427, 1393, 1368, 1331; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11-8.05 (2H, m, Ar**H**), 7.76 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.69-7.64 (1H, m, Ar**H**), 7.49-7.46 (1H, m, Ar**H**), 7.41 (1H, d, *J* = 8.5 Hz, Ar**H**), 4.04 (1H, q, *J* = 7.0 Hz, C**H**CH_3), 1.59 (3H, d, *J* = 7.5 Hz, CHC**H**$_3$), 1.40 (9H, s, C(C**H**$_3$)$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 172.7 (C), 160.6 (C), 147.6 (C), 136.4 (CH), 129.3 (CH), 129.1 (CH), 127.3(CH), 126.9 (C), 126.0 (CH), 119.7 (CH), 80.7 (C), 49.6 (CH), 27.8 (3 x CH_3), 17.3 (CH_3); HRMS (ES) Exact mass calcd for $C_{16}H_{20}NO_2$ $[M+H]^+$: 258.1489, found: 258.1488.

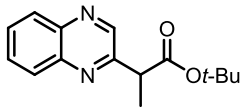
***tert*-Butyl 2-(isoquinolin-1-yl)propanoate 2.65**



General procedure A was applied to 1-chloroisoquinoline (500 mg, 3.06 mmol), *tert*-butyl propionate (1.38 mL, 9.17 mmol) and NaHMDS

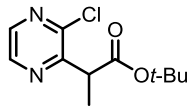
(0.6 M in toluene, 15.3 mL, 9.17 mmol). The reaction was stirred for 2 h and purified by flash chromatography (*n*-hexane/EtOAc 19:1→4:1) to give *azaarylacetate* **2.65** (637 mg, 81%) as an orange solid. R_f 0.58 (*n*-hexane/EtOAc 4:1), m.p. 34 °C; IR (film, cm^{-1}) 3055, 2979, 2934, 1731 (C=O), 1625, 1587, 1562, 1503, 1368, 1319, 1158; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (1H, d, *J* = 5.5 Hz, Ar**H**), 8.18 (1H, d, *J* = 8.5 Hz, Ar**H**), 7.84 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.70-7.66 (1H, m, Ar**H**), 7.65-7.59 (1H, m, Ar**H**), 7.56 (1H, d, *J* = 5.6 Hz, Ar**H**), 4.61 (1H, q, *J* = 7.0 Hz, C**H**CH_3), 1.68 (3H, d, *J* = 7.0 Hz, CHC**H**$_3$), 1.36 (9H, s, C(C**H**$_3$)$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 172.9 (C), 160.0 (C), 142.0 (CH), 136.5 (C), 129.7 (CH), 127.5 (CH), 127.1 (CH), 126.6 (C), 124.8 (CH), 119.8 (CH), 80.8 (C), 45.4 (CH), 27.9 (3 x CH_3), 16.4 (CH_3); HRMS (ES) Exact mass calcd for $C_{16}H_{20}NO_2$ $[M+H]^+$: 258.1489, found: 258.1488.

***tert*-Butyl 2-(quinoxalin-2-yl)propanoate 2.66**[126]



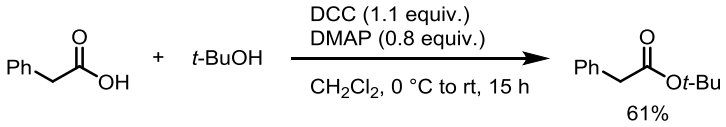
General procedure A was applied to 2-chloroquinoxaline (100 mg, 0.608 mmol), *tert*-butyl propionate (270 μL, 1.82 mmol) and NaHMDS (0.6 M in toluene, 3.03 mL, 1.82 mmol). The reaction was stirred for 2 h and purified by flash chromatography (*n*-hexane/Et_2O 19:1→4:1) to give azaarylacetate **2.66** (106 mg, 67%) as a yellow oil. R_f 0.34 (*n*-hexane/EtOAc 9:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.87 (1H, s, Ar**H**), 8.12-8.07 (2H, m, Ar**H**), 7.79-7.73 (2H, m, Ar**H**), 4.09 (1H, q, *J* = 7.5 Hz, C**H**CH_3), 1.67 (3H, d, *J* = 7.5 Hz, CHC**H**$_3$), 1.43 (9H, s, C(C**H**$_3$)$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 171.8 (C), 155.4 (C), 145.2 (CH), 142.0 (C), 141.4 (C), 130.0 (CH), 129.5 (CH), 129.2 (CH), 129.1 (CH), 81.6 (C), 47.5 (CH), 28.0 (3 x CH_3), 16.6 (CH_3). Data consistent with literature.[126]

***tert*-Butyl 2-(3-chloropyrazin-2-yl)propanoate 2.67[316]**



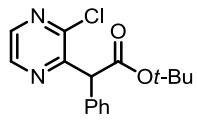
General procedure B was applied to 2,3-dichloropyrazine (500 mg, 3.36 mmol), NaHMDS (0.6 M in toluene, 12.3 mL, 7.39 mmol) and *tert*-butyl propionate (560 µL, 3.69 mmol). The product was purified by flash chromatography (pet. ether/EtOAc 19:1→9:1) to give azaarylacetate **2.67** (548 mg, 67%) as a yellow oil. R_f 0.35 (pet. ether/EtOAc 9:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (1H, d, *J* = 2.5 Hz, Ar**H**), 8.27 (1H, d, *J* = 2.5 Hz, Ar**H**), 4.23 (1H, q, *J* = 7.0 Hz, C**H**CH_3), 1.57 (3H, d, *J* = 7.0 Hz, CHC**H**$_3$), 1.41 (9H, s, C(C**H**$_3$)$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 171.2 (C), 154.7 (C), 148.9 (C), 142.0 (CH), 142.0 (CH), 81.6 (C), 45.4 (CH), 27.9 (3 x CH_3), 15.1 (CH_3). Data consistent with literature.[316]

***tert*-Butyl 2-phenylacetate 6.02[321]**



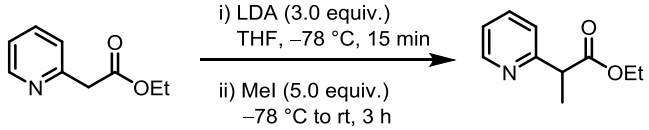
To a solution of DCC (1.67 g, 8.07 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added DMAP (658 mg, 5.87 mmol) and phenylacetic acid (1.00 g, 7.34 mmol). To the suspension was added *t*-BuOH (2.10 mL, 22.0 mmol) and the reaction warmed to room temperature. The reaction was stirred for 16 h and concentrated *in vacuo*. The residue was washed with Et_2O and filtered through celite. The filtrate was washed with 1 N NaOH (40 mL), 1 N HCl (40 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by flash chromatography (pet. ether/EtOAc 19:1→9:1) to give ester **6.02** (861 mg, 61%) as a pale pink oil. R_f 0.69 (pet. ether/Et_2O 9:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.32 (2H, m, Ar**H**), 7.32-7.26 (3H, m, Ar**H**), 3.56 (2H, s, C**H**$_2$Ph), 1.47 (9H, s, CO_2C(C**H**$_3$)$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 170.9 (C), 134.7 (C), 129.2 (2 x CH), 128.4 (2 x CH), 126.8 (CH), 80.7 (C), 42.6 (CH_2), 28.0 (3 x CH_3). Data consistent with literature.[321]

***tert*-Butyl 2-(3-chloropyrazin-2-yl)-2-phenylacetate 2.68**[316]



General procedure B was applied to 2,3-dichloropyrazine (476 mg, 3.19 mmol), NaHMDS (0.6 M in toluene, 11.7 mL, 7.02 mmol) and *tert*-butyl 2-phenyl acetate **6.02** (675 mg, 3.51 mmol). The product was purified by flash chromatography (pet. ether/Et_2O 19:1→4:1) to give azaarylacetate **2.68** (612 mg, 63%) as a viscous yellow oil. R_f 0.20 (pet. ether/EtOAc 9:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (1H, d, *J* = 2.5 Hz, Ar**H**), 8.28 (1H, d, *J* = 2.5 Hz, Ar**H**), 7.40-7.29 (5H, m, Ar**H**), 5.46 (1H, s, C**H**Ph), 1.44 (9H, s, C(C**H**$_3$)$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 169.0 (C), 153.4 (C), 149.1 (C), 142.1 (CH), 142.0 (CH), 135.0 (C), 129.7 (2 x CH), 128.4 (2 x CH), 127.8 (CH), 82.2 (C), 56.6 (CH), 27.9 (3 x CH_3). Data consistent with literature.[316]

Ethyl 2-(pyridin-2-yl)propanoate 2.70[127]

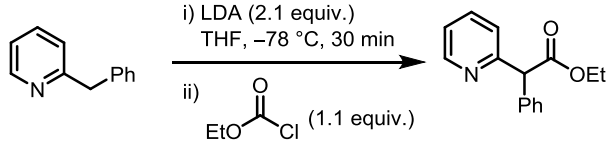


2.69 **2.70** 68%

To a stirred solution of diisopropylamine (1.27 mL, 9.09 mmol) in THF (3 mL) at −78 °C was added *n*-BuLi (1.6 M in hexanes, 5.68 mL, 9.09 mmol) dropwise and the mixture stirred for 15 min. To the mixture was added pyridyl ester **2.69** (460 μL, 3.03 mmol), the mixture stirred for 15 min, and iodomethane (940 μL, 15.2 mmol) added. The reaction was stirred for 15 min, warmed to room temperature and stirred for 3 h. The mixture was diluted with water (10 mL), the phases separated, and the aqueous phase extracted with EtOAc (3 x 10 mL). The combined organics were dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash chromatography (*n*-hexane/EtOAc 9:1→4:1) to give azaarylacetate **2.70** as a yellow oil (370 mg, 68%). R_f 0.36 (*n*-hexane/EtOAc 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (1H, d, *J* = 5.0 Hz, Ar**H**), 7.65 (1H, dt, *J* = 7.5, 1.5 Hz), 7.30-7.26 (1H, m, Ar**H**), 7.19-7.14 (1H, m, Ar**H**), 4.22-4.10 (2H, m, C**H**$_2$CH$_3$), 3.93 (1H, q, *J* = 7.0 Hz, C**H**CH$_3$), 1.55 (3H, d, *J* = 7.0 Hz, CHC**H**$_3$), 1.20 (3H, t, *J* = 7.0 Hz, CH$_2$C**H**$_3$); ^{13}C NMR

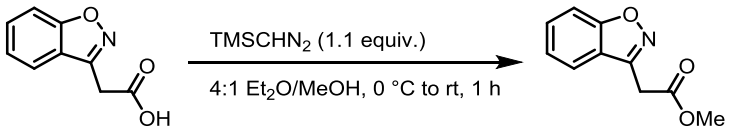
(100 MHz, $CDCl_3$) δ 173.6 (C), 160.0 (C), 149.3 (CH), 136.7 (CH), 122.0 (CH), 121.9 (CH), 60.8 (CH), 48.0 (CH_2), 17.2 (CH_3), 14.1 (CH_3). Data consistent with literature.[127]

Ethyl 2-phenyl-2-(pyridin-2-yl)acetate 2.72[322]



To a stirred solution of diisopropylamine (1.74 mL, 12.4 mmol) in THF (30 mL) at −78 °C was added *n*-BuLi (1.6 M in hexanes, 7.76 mL, 12.4 mmol) dropwise and the mixture stirred for 30 min. To the mixture was added 2-benzylpyridine **2.70** (0.95 mL, 5.9 mmol), the mixture stirred for 30 min, and ethyl chloroformate (0.62 mL, 6.5 mmol) added. The reaction was stirred for 15 min, warmed to room temperature and stirred for 1.5 h. The mixture was diluted with water (30 mL) and the THF removed *in vacuo*. EtOAc (30 mL) was added, the phases separated, and the aqueous phase extracted with EtOAc (3 x 30 mL). The combined organics were dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash chromatography (pet. ether/EtOAc 99:1→3:1) to give azaarylacetate **2.72** as a yellow oil (1.09 g, 76%). R_f 0.39 (pet. ether/EtOAc 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60-5.57 (1H, m, Ar**H**), 7.64-7.59 (1H, m, Ar**H**), 7.43-7.39 (2H, m, Ar**H**), 7.38-7.33 (2H, m, Ar**H**), 7.32-7.27 (1H, m, Ar**H**), 7.27-7.24 (1H, m, Ar**H**), 7.19-7.15 (1H, m, Ar**H**), 5.24 (1H, s, C**H**Ph), 4.27-4.22 (2H, m, C**H**$_2$CH$_3$), 1.26 (3H, t, *J* = 7.0 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7 (C), 158.7 (C), 149.2 (CH), 137.3 (C), 136.6 (CH), 128.9 (2 x CH), 128.7 (2 x CH), 127.5 (CH), 123.0 (CH), 122.1 (CH), 61.3 (CH_2), 59.7 (CH), 14.1 (CH_3). Data consistent with literature.[322]

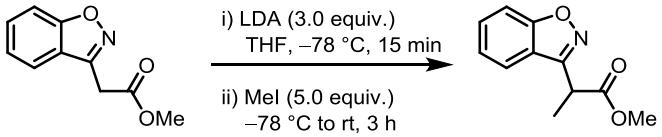
Methyl 2-(1,2-benzoxazol-3-yl)acetate 2.74[323]



2.73 **2.74** 66%

To a stirred solution of benzisoxazole acid **2.73** (300 mg, 1.69 mmol) in Et_2O (10 mL) and MeOH (2 mL) at 0 °C was added (trimethylsilyl)diazomethane (2.0 M in Et_2O, 0.93 mL, 1.86 mmol). The reaction was warmed to room temperature, stirred for 1 h and the solvent was removed *in vacuo*. The product was purified by flash chromatography (*n*-hexane/EtOAc 19:1→9:1) to give azaarylacetate **2.74** (212 mg, 66%) as a pale yellow oil. R_f 0.43 (*n*-hexane/EtOAc 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (1H, dt, *J* = 8.0, 1.0 Hz, Ar**H**), 7.62-7.55 (2H, m, Ar**H**), 7.34 (1H, ddd, *J* = 8.0, 6.0, 2.0 Hz, Ar**H**), 4.07 (2H, s, C**H**$_2$), 3.76 (3H, s, C**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7 (C), 163.4 (C), 152.4 (C), 130.0 (CH), 123.7 (CH), 121.6 (CH), 121.2 (C), 110.0 (CH), 52.6 (CH_2), 31.4 (CH_3). Data consistent with literature.[323]

Methyl 2-(1,2-benzoxazol-3-yl)propanoate 2.75[324]

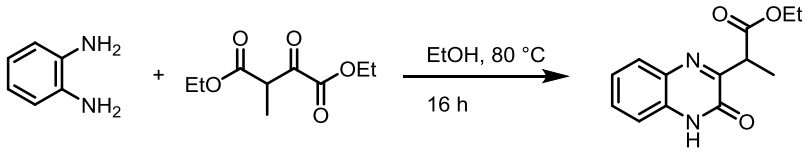


2.74 **2.75** 36%

To a stirred solution of diisopropylamine (0.47 mL, 3.33 mmol) in THF (5 mL) at −78 °C was added *n*-BuLi (1.6 M in hexanes, 2.08 mL, 3.33 mmol) dropwise and the mixture stirred for 15 min. To the mixture was added benzisoxazole ester **2.74** (206 mg, 1.11 mmol), the mixture stirred for 15 min and iodomethane (0.35 mL, 5.54 mmol) added. The reaction was stirred for 15 min, warmed to room temperature and stirred for 3 h. The mixture was diluted with water (10 mL), the phases separated, and the aqueous phase extracted with EtOAc (3 x 10 mL). The combined organics were dried ($MgSO_4$) and the solvent removed *in vacuo*.

The product was purified by flash chromatography (*n*-hexane/EtOAc 19:1→4:1) to give azaarylacetate **2.75** as a pale yellow oil (81 mg, 36%). R_f 0.86 (*n*-hexane/EtOAc 3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.52-7.59 (2H, m, Ar**H**), 7.31 (1H, ddd, *J* = 8.0, 6.5, 1.0 Hz, Ar**H**), 4.29 (1H, q, *J* = 7.5 Hz, C**H**CH_3), 3.71 (3H, s, OC**H**$_3$), 1.73 (3H, d, *J* = 7.0 Hz, CHC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 172.0 (C), 163.4 (C), 157.0 (C), 129.9 (CH), 123.5 (CH), 121.8 (CH), 120.2 (C), 110.0 (CH), 52.5 (CH_3), 37.8 (CH), 15.7 (CH_3). Data consistent with literature.[324]

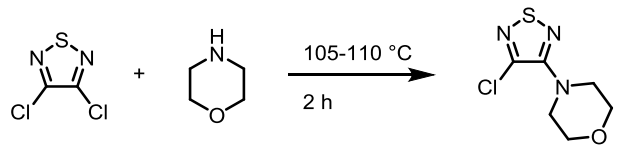
Ethyl 2-(3-oxo-3,4-dihydroquinoxalin-2-yl)propanoate 2.78[128]



2.76 **2.77** **2.78** 76%

To *o*-phenylenediamine **2.76** (1.00 g, 9.25 mmol) in EtOH (15 mL) at 80 °C under nitrogen was added diethyl oxalpropionate **2.77** (1.74 mL, 9.25 mmol) and the reaction was heated at reflux for 16 h. Water (5 mL) was added to the hot solution until it became cloudy. The mixture was allowed to cool to room temperature and then to 0 °C. The resultant solid was collected by filtration and washed with a cold EtOH/water 2:1 solution (100 mL). The product was purified by flash chromatography ($CHCl_3$/EtOAc 9:1) to give azaarylacetate **2.78** as a white solid (1.74 g, 76%). R_f 0.31 (pet. ether/EtOAc 2:1); m.p. 150 °C (lit. 160-162 °C)[325]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.17 (1H, s, N**H**), 7.88 (1H, dd, *J* = 8.0, 1.0 Hz, Ar**H**), 7.55-7.51 (1H, m, Ar**H**), 7.39-7.34 (1H, m, Ar**H**), 7.32 (1H, dd, *J* = 8.0, 1.0 Hz, Ar**H**), 4.27 (1H, q, *J* = 7.0 Hz, C**H**CH_3), 4.25-4.17 (2H, m, C**H**$_2$$CH_3$), 1.66 (3H, d, *J* = 7.0 Hz, CHC**H**$_3$), 1.24 (3H, t, *J* = 7.0 Hz, CH_2C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 172.6 (C), 158.9 (C), 155.8 (C), 132.6 (C), 131.1 (C), 130.3 (CH), 129.3 (CH), 124.3 (CH), 115.6 (CH), 61.0 (CH_2), 43.7 (CH), 14.3 (CH_3), 14.2 (CH_3). Data consistent with literature.[128]

4-(4-Chloro-1,2,5-thiadiazol-3-yl)morpholine 2.81[129]

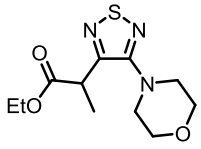


2.79 **2.80** **2.81** 68%

To stirred morpholine **2.80** (2.26 mL, 25.8 mmol) at 105-110 °C was added 3,4-dichloro-1,2,5-thiadiazole **2.79** (610 µL, 6.45 mmol) dropwise over 30 minutes. The reaction was stirred for 2 h, cooled to room temperature and diluted with water (25 mL). The mixture was made acidic with conc. HCl (25 mL) and the product precipitated out of solution. The product was isolated by filtration and washed with water to give thiadiazole **2.81** (901 mg, 68%) as a light yellow powder. R_f 0.55 (pet. ether/EtOAc 4:1); m.p. 38-40 °C (lit. 43-45 °C)[129]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.87-3.83 (4H, m, O(C**H**$_2$CH$_2$)$_2$N), 3.50-3.46 (4H, m, O(CH$_2$C**H**$_2$)$_2$N); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 158.9 (C), 135.2 (C), 66.3 (CH_2), 49.1 (CH_2). Data consistent with literature.[130]

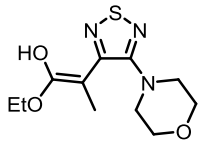
Ethyl 2-[4-(morpholin-4-yl)-1,2,5-thiadiazol-3-yl]propanoate 2.82

General procedure C was applied to **2.81** (100 mg, 0.49 mmol), LiHMDS (1.0 M in THF, 1.1 mL, 1.1 mmol) and ethyl propionate (60 µL, 0.54 mmol). The product was purified by flash chromatography (pet. ether/EtOAc 9:1→1:1) to give *azaarylacetate* **2.82** (ester: yellow oil, 66 mg and enol: yellow oil, 37 mg, 78% combined yield).



Ester: R_f 0.37 (pet. ether/EtOAc 4:1); IR (film, cm^{-1}) 2965, 2855, 1734 (C=O), 1495, 1449, 1431, 1369, 1302, 1246, 1198; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.21-4.11 (2H, m, C**H**$_2$CH$_3$), 3.94 (1H, q, *J* = 7.0 Hz, C**H**CH$_3$), 3.85-3.77 (4H, m, O(C**H**$_2$CH$_2$)$_2$N), 3.28-3.17 (4H, m, O(CH$_2$C**H**$_2$)$_2$N), 1.62 (3H, d, *J* = 7.0 Hz, CHC**H**$_3$), 1.20 (3H, t, *J* = 7.0 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 171.9 (C), 162.8 (C), 153.5 (C), 66.5 (2 x CH_2), 61.3 (CH_2), 50.7 (2 x CH_2), 41.0 (CH), 16.6 (CH_3), 14.0 (CH_3); HRMS (ES) Exact mass calcd for $C_{11}H_{18}N_3O_3S$ $[M+H]^+$: 272.1063,

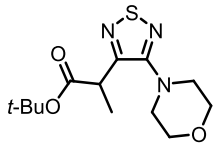
found: 272.1067.



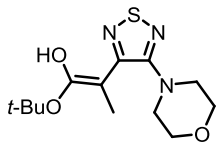
Enol: R_f 0.20 (pet. ether/EtOAc 4:1); IR (film, cm^{-1}) 3410 (OH), 2963, 2855, 1738, 1491, 1449, 1427, 1373, 1258, 1204; ^1H NMR (500 MHz, $CDCl_3$) δ 4.40 (1H, s, O**H**), 4.31 (1H, qd, *J* = 10.5, 7.0 Hz, C**H**$_a$CH$_b$CH$_3$), 4.21 (1H, dq, *J* = 10.5, 7.0 Hz, CH$_a$C**H**$_b$CH$_3$), 3.82 (2H, ddd, *J* = 11.5, 6.5, 3.0 Hz, O(C**H**$_2$CH$_2$)N), 3.75 (2H, ddd, *J* = 11.5, 6.5, 3.0 Hz, O(C**H**$_2$CH$_2$)N), 3.42-3.36 (2H, m O(CH$_2$C**H**$_2$)N), 3.08-3.02 (2H, m, O(CH$_2$CH$_2$)N), 1.93 (3H, s, C=CC**H**$_3$), 1.23 (3H, t, *J* = 7.0 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 174.4 (C), 162.2 (C), 155.0 (C), 73.2 (C), 66.6 (2 x CH_2), 62.5 (CH_2), 51.8 (2 x CH_2), 25.5 (CH_3), 14.0 (CH_3); HRMS (ES) Exact mass calcd for $C_{11}H_{18}N_3O_3S$ $[M+H]^+$: 272.1063, found: 272.1067.

***tert*-Butyl 2-[4-(morpholin-4-yl)-1,2,5-thiadiazol-3-yl]propanoate 2.83**

General procedure C was applied to **2.36** (1.00 g, 4.86 mmol), LiHMDS (1.0 M in THF, 11.2 mL, 11.2 mmol) and *tert*-butyl propionate (0.80 mL, 5.4 mmol). The product was purified by flash chromatography (pet. ether/EtOAc 9:1→3:1) to give *azaarylacetate* **2.83** (ester: yellow solid, 1.20 g and enol: yellow solid, 49 mg, 86% combined yield).



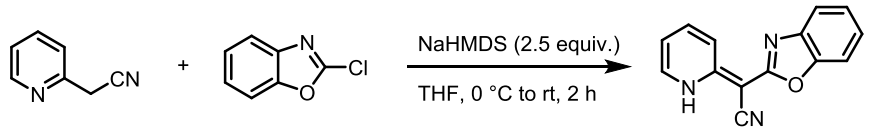
Ester: R_f 0.82 (pet. ether/EtOAc 4:1); m.p. 56-58 °C; IR (film, cm^{-1}) 2976, 2855, 1730 (C=O), 1495, 1450, 1431, 1368, 1267, 1250, 1146; ^1H NMR (500 MHz, $CDCl_3$) δ 3.89-3.80 (5H, m, C**H**CH$_3$, O(C**H**$_2$CH$_2$)$_2$N), 3.33-3.27 (2H, m, O(CH$_2$C**H**$_2$)N), 3.26-3.20 (2H, m, O(CH$_2$C**H**$_2$)N), 1.61 (3H, d, *J* = 7.0 Hz, CHC**H**$_3$), 1.42 (9H, s, C(C**H**$_3$)$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 171.2 (C), 162.8 (C), 153.9 (C), 81.6 (C), 66.5 (2 x CH_2), 50.7 (2 x CH_2), 42.0 (CH), 27.9 (3 x CH_3), 16.6 (CH_3); HRMS (ES) Exact mass calcd for $C_{13}H_{22}N_3O_3S$ $[M+H]^+$: 300.1376, found: 300.1380.



Enol: R_f 0.71 (pet. ether/EtOAc 4:1); m.p. 76-78 °C; IR (film, cm^{-1}) 3435 (OH), 2978, 2859, 1732, 1491, 1450, 1425, 1258, 1206, 1138; ^1H NMR (500 MHz, $CDCl_3$) δ 4.39 (1H, s, O**H**), 3.83-3.73 (4H, m,

O(C**H**$_2$CH$_2$)$_2$N), 3.46-3.40 (2H, m, O(CH$_2$C**H**$_2$)N), 3.14-3.07 (2H, m, O(CH$_2$C**H**$_2$)N), 1.87 (3H, s, C=CC**H**$_3$), 1.41 (9H, s, C(C**H**$_3$)$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 173.3 (C), 163.2 (C), 155.0 (C), 83.2 (C), 73.5 (C), 66.4 (2 x CH_2), 51.7 (2 x CH_2), 27.8 (3 x CH_3), 25.6 (CH_3); HRMS (ES) Exact mass calcd for $C_{13}H_{20}N_3O_3S$ $[M-H]^+$: 298.1220, found: 298.1221.

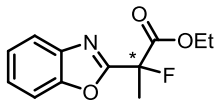
2-(1,3-Benzoxazol-2-yl)-2-[(2*E*)-1,2-dihydropyridin-2-ylidene]acetonitrile 2.88



2.87 **2.85** **2.88** 97%

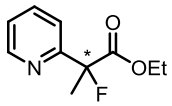
To a stirred solution of 2-pyridylacetonitrile **2.87** (0.94 mL, 8.46 mmol) and 2-chlorobenzoxazole **2.85** (1.06 mL, 9.31 mmol) in THF (40 mL) at 0 °C under nitrogen was added NaHMDS (1.0 M in THF, 21.2 mL, 21.2 mmol). The reaction was warmed to room temperature and stirred for 2 h. The reaction was quenched with sat. aq. NH_4Cl (40 mL), the phases separated, and the aqueous phase extracted with EtOAc (3 x 40 mL). The combined organics were dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash chromatography (CH_2Cl_2) to give *pyridyl benzoxazole* **2.88** as a bright yellow solid (1.93 g, 97%). R_f (CH_2Cl_2) 0.60; m.p. 154 °C; IR (film, cm^{-1}) 2191 (C≡N), 1635, 1599, 1552, 1508, 1450, 1410, 1371, 1321, 1250; ^{1}H NMR (500 MHz, $CDCl_3$) δ 15.52 (1H, s, N**H**), 7.79 (1H, d, *J* = 6.5 Hz, Ar**H**), 7.60-7.56 (1H, m, Ar**H**), 7.52-7.45 (3H, m, Ar**H**), 7.30-7.25 (1H, m, Ar**H**), 7.23-7.19 (1H, m, Ar**H**), 6.67 (1H, dt, *J* = 6.5, 1.0 Hz, Ar**H**); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 164.1 (C), 152.4 (C), 148.5 (C), 140.9 (C), 138.4 (CH), 134.1 (CH), 124.2 (CH), 123.0 (CH), 120.8 (CH), 118.6 (C), 116.5 (CH), 111.9 (CH), 110.1 (CH), 59.5 (C); HRMS (ES) Exact mass calcd for $C_{14}H_{10}N_3O$ $[M+H]^+$: 236.0818, found: 236.0817.

Ethyl 2-(1,3-benzoxazol-2-yl)-2-fluoropropanoate 2.89



General procedure D was applied to **2.59** (22 mg, 0.10 mmol), [((*R*)-BINAP)Pd$(OH_2)_2$]$^{2+}$2OTf$^-$ (5 mg, 5 mol%) and NFSI (34 mg, 0.11 mmol) at –20°C. The product was purified as described above (pet. ether/EtOAc 19:1→9:1) to give *2-fluoroazaarylacetate* **2.89** (10 mg, 42%) as a colourless oil. R_f 0.50 (*n*-hexane/EtOAc 9:1); $[\alpha]_D^{25}$ +20.2 (*c* 0.52, $CHCl_3$); IR (film, cm^{-1}) 2925, 2853, 1771 (C=O), 1454, 1266, 1136, 1115, 1097 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83-7.80 (1H, m, Ar**H**), 7.61-7.58 (1H, m, Ar**H**), 7.46-7.38 (2H, m, Ar**H**), 4.41-4.30 (2H, m, C**H**$_2$CH$_3$), 2.18 (3H, d, *J* = 22.0 Hz, CFC**H**$_3$), 1.32 (3H, t, *J* = 7.0 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 167.4 (C, d, *J* = 27.5 Hz), 160.6 (C, d, *J* = 25.0 Hz), 150.9 (C), 140.3 (C), 126.4 (CH), 125.0 (CH), 121.0 (CH), 111.2 (CH), 89.8 (C, d, *J* = 187.5 Hz), 62.9 (CH$_2$), 21.9 (CH$_3$, d, *J* = 23.0 Hz), 14.0 (CH$_3$); ^{19}F NMR (376 MHz, $CDCl_3$) δ −150.2; HRMS (ES) Exact mass calcd for $C_{12}H_{13}FNO_3$ $[M+H]^+$: 238.0874, found: 238.0880; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (99.5:0.5 hexane:*i*-PrOH, 0.8 mL/min, 254 nm, 25 °C); t_r (major) = 15.2 min; t_r (minor) = 16.4 min; 93% *ee*.

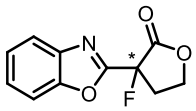
Ethyl 2-fluoro-2-(pyridin-2-yl)propanoate 6.03



General procedure D was applied to **2.70** (10 mg, 50 μmol), [((*R*)-BINAP)Pd$(OH_2)_2$]$^{2+}$2OTf$^-$ (3 mg, 5 mol%) and NFSI (17 mg, 55 μmol) at room temperature. The product was purified as described above (pet. ether/Et_2O 9:1→3:1) to give *2-fluoroazaarylacetate* **6.03** (22% conv.) as a colourless oil. R_f 0.26 (pet. ether/Et_2O 3:1); IR (film, cm^{-1}) 2991, 2962, 2925, 2854, 1751 (C=O), 1590, 1472, 1435, 1267, 1135, 1100, 1022; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64-8.60 (1H, m, Ar**H**), 7.78 (1H, dt, *J* = 8.0, 2.0 Hz, Ar**H**), 7.64-7.61 (1H, m, Ar**H**), 7.30 (1H, ddd, *J* = 7.5, 5.0, 1.0 Hz, Ar**H**), 4.31-4.21 (2H, m, C**H**$_2$CH$_3$), 2.00 (3H, d, *J* = 22.5 Hz, CFC**H**$_3$, 1.26 (3H, t, *J* = 7.0 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 169.7 (d, *J* = 26.0 Hz, C), 157.8 (d, *J* = 26.5 Hz,

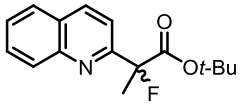
C), 148.9 (CH), 137.1 (CH), 123.5 (CH), 119.7 (d, *J* = 7.5 Hz, CH), 95.7 (d, *J* = 184.0 Hz, C), 62.1 (CH_2), 23.1 (d, *J* = 23.0 Hz, CH_3), 14.0 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ −152.3; HRMS (ES) Exact mass calcd for $C_{10}H_{13}FNO_2$ $[M+H]^+$: 198.0925, found: 198.0927; Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (97:3 hexane:*i*-PrOH, 0.8 mL/min, 254 nm, 25 °C); t_r (major) = 8.9 min, t_r (minor) = 9.9 min; 14% *ee*.

3-(1,3-Benzoxazol-2-yl)-3-fluorooxolan-2-one 2.96



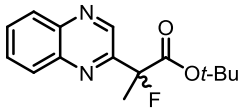
General procedure D was applied to **2.62** (20 mg, 0.10 mmol), [((*R*)-BINAP)Pd$(OH_2)_2]^{2+}2OTf^-$ (5 mg, 5 mol%) and NFSI (34 mg, 1.1 mmol) at room temperature. The product was purified as described above (pet. ether/EtOAc 9:1→4:1) to give *2-fluoroazaarylacetate* **2.96** (14 mg, 63%) as a cream solid. R_f 0.29 (pet. ether/EtOAc 4:1); $[\alpha]_D^{25}$ +7.9 (c 0.70, $CHCl_3$); m.p. 100 °C; IR (film, cm^{-1}) 2926, 1796 (C=O), 1614, 1566, 1477, 1452, 1379, 1352, 1304, 1238; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81-7.78 (1H, m, Ar**H**), 7.67-7.64 (1H, m, Ar**H**), 7.49-7.41 (2H, m, Ar**H**), 4.69-4.57 (2H, m, $CO_2C\mathbf{H}_2CH_2CF$), 3.45 (1H, dddd, *J* = 14.0, 13.0, 7.0, 4.0 Hz, $CO_2CH_2C\mathbf{H}_aH_bCF$), 2.99 (1H, ddt, *J* = 22.0, 14.0, 8.0 Hz, $CO_2CH_2CH_a\mathbf{H}_bCF$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 168.2 (d, *J* = 26.0 Hz, C), 157.5 (d, *J* = 28.0 Hz, C), 151.4 (C), 140.1 (C), 126.8 (CH), 125.3 (CH), 120.9 (CH), 111.5 (CH), 89.5 (d, *J* = 195.0 Hz, C), 65.2 (d, *J* = 4.5 Hz, CH_2), 33.8 (d, *J* = 20.5 Hz, CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ −161.6; HRMS (ES) Exact mass calcd for $C_{11}H_9FNO_3$ $[M+H]^+$: 222.0561, found: 222.0568; Enantiomeric excess was determined by HPLC with a Chiralpak IA-3 column (99:1 hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C); t_r (major) = 17.1 min; t_r (minor) = 18.6 min; 93% *ee*.

***tert*-Butyl 2-fluoro-2-(quinolin-2-yl)propanoate 6.04**



General procedure D was applied to **2.64** (13 mg, 49 μmol), [((*R*)-BINAP)Pd$(OH_2)_2]^{2+}2OTf^-$ (3 mg, 5 mol%) and NFSI (17 mg, 1.1 mmol) at room temperature. The product was purified as described above (pet. ether/Et_2O 19:1) to give *2-fluoroazaarylacetate* **6.04** (89% conv.) as a colourless oil. R_f 0.64 (pet. ether/EtOAc 9:1); IR (film, cm^{-1}) 2982, 2932, 1746 (C=O), 1620, 1299, 1504, 1450, 1369, 1290, 1258; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (1H, d, *J* = 8.5 Hz, Ar**H**), 8.12 (1H, d, *J* = 8.5 Hz, Ar**H**), 7.84 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.73 (1H, ddd, *J* = 8.5, 7.0, 1.5 Hz, Ar**H**), 7.69 (1H, dd, *J* = 8.5, 1.0 Hz, Ar**H**), 7.60-7.55 (1H, m, Ar**H**), 2.06 (3H, d, *J* = 22.5 Hz, CFC$\mathbf{H}_3$), 1.46 (9H, s, C(C$\mathbf{H}_3)_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 168.9 (d, *J* = 25.5 Hz, C), 158.1 (d, *J* = 26.5 Hz, C), 147.1 (C), 136.9 (CH), 129.8 (CH), 129.6 (CH), 127.6 (C), 127.5 (CH), 126.9 (CH), 117.4 (d, *J* = 6.0 Hz, CH), 96.3 (d, *J* = 183.5 Hz, C), 82.8 (C), 27.8 (3 x CH_3), 22.7 (d, *J* = 23.5 Hz, CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ −149.9; HRMS (ES) Exact mass calcd for $C_{16}H_{19}FNO_2$ $[M+H]^+$: 276.1394, found: 276.1393; Enantiomeric excess was determined by HPLC with a Chiralpak IC-3 column (99:1 hexane:*i*-PrOH, 0.8 mL/min, 230 nm, 25 °C); t_r = 16.4 min; t_r = 24.3 min; 0% *ee*.

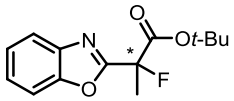
***tert*-Butyl 2-fluoro-2-(quinoxalin-2-yl)propanoate 6.05**



General procedure D was applied to **2.66** (13 mg, 49 μmol), [((*R*)-BINAP)Pd$(OH_2)_2]^{2+}2OTf^-$ (3 mg, 5 mol%) and NFSI (17 mg, 54 μmol) at room temperature. The product was purified as described above (*n*-hexane/EtOAc 19:1→9:1) to give *2-fluoroazaarylacetate* **6.05** (45% conv.) as a colourless oil. R_f 0.26 (*n*-hexane/EtOAc 9:1); IR (film, cm^{-1}) 2978, 2931, 2868, 1753 (C=O), 1374, 1178, 1127, 1081; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.12 (1H, s, Ar**H**), 8.18-8.10 (2H, m, Ar**H**), 7.85-7.78 (2H, m, Ar**H**), 2.09 (3H, d, *J* = 22.5 Hz, CFC$\mathbf{H}_3$), 1.46 (9H, s, C(C$\mathbf{H}_3)_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 168.0 (d, *J* = 25.5 Hz, C), 152.6 (d, *J* = 26.5 Hz, C), 142.4 (d, *J* = 7.0 Hz, CH), 142.1 (C), 141.1 (C), 130.5 (CH), 130.4 (CH), 129.7 (CH), 129.2 (CH),

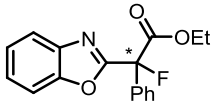
95.5 (d, *J* = 186.5 Hz, C), 83.5 (C), 27.8 (3 x CH_3), 22.3 (d, *J* = 23.0 Hz, CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ −151.7; HRMS (ES) Exact mass calcd for $C_{15}H_{18}FN_2O_2$ $[M+H]^+$: 277.1347, found: 277.1346; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (98:2 hexane:*i*-PrOH, 0.8 mL/min, 230 nm, 25 °C); t_r = 8.9 min; t_r = 9.7 min; 0% *ee*.

tert-Butyl 2-(1,3-benzoxazol-2-yl)-2-fluoropropanoate 5.01



General procedure D was applied to **2.60** (25 mg, 0.10 mmol), [((*R*)-BINAP)Pd$(OH_2)_2]^{2+}2OTf^-$ (5 mg, 5 mol%) and NFSI (34 mg, 0.11 mmol) at −20 °C. The product was purified as described above (pet. ether/Et_2O 19:1→9:1) to give *2-fluoroazaarylacetate* **5.01** (19 mg, 72%) as a white solid. R_f 0.50 (*n*-hexane/EtOAc 3:1); $[\alpha]_D^{25}$ +15.1 (*c* 0.96 , $CHCl_3$); m.p. 100 °C; IR (film, cm^{-1}) 2958, 2925, 2854, 1765 (C=O), 1454, 1373, 1265, 1136, 1114, 1096; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84-7.80 (1H, m, Ar**H**), 7.62-7.58 (1H, m, Ar**H**), 7.46-7.38 (2H, m, Ar**H**), 2.15 (3H, d, *J* = 21.5 Hz, CFC**H**$_3$), 1.51 (9H, s, C(C**H**$_3$)$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 166.3 (d, *J* = 27.0 Hz, C), 161.1 (d, *J* = 25.0 Hz, C), 150.9 (C), 140.3 (C), 126.2 (CH), 124.8 (CH), 120.9 (CH), 111.1 (CH), 89.7 (d, *J* = 187.0, C), 84.3 (C), 27.8 (3 x CH_3), 21.7 (d, *J* = 23.0 Hz, CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –149.3; HRMS (ES) Exact mass calcd for $C_{14}H_{17}FNO_3$ $[M+H]^+$: 266.1187, found: 266.1185; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (99.5:0.5 hexane:*i*-PrOH, 0.8 mL/min, 254 nm, 25 °C); t_r (major) = 9.6 min, t_r (minor) = 10.4 min; 90% *ee*.

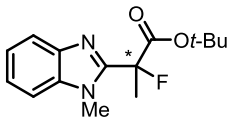
Ethyl 2-(1,3-benzoxazol-2-yl)-2-fluoro-2-phenylacetate 5.02



General procedure D was applied to **2.61** (28 mg, 0.1 mmol), [((*R*)-BINAP)Pd$(OH_2)_2]^{2+}2OTf^-$ (5 mg, 5 mol%) and NFSI (34 mg, 0.11 mmol) at −20 °C. The product was purified as described above (pet. ether/Et_2O 19:1→4:1) to give *2-fluoroazaarylacetate* **5.02** (24 mg, 80%) as a colourless oil. R_f 0.69

(pet. ether/EtOAc 4:1); $[\alpha]_D^{25}$ + 7.5 (*c* 1.20, $CHCl_3$); IR (film, cm^{-1}) 1765 (C=O), 1612, 1566, 1497, 1452, 1369, 1346, 1240, 1175, 1092; ^1H NMR (500 MHz, $CDCl_3$) δ 7.84-7.81 (1H, m, Ar**H**), 7.71-7.67 (2H, m, Ar**H**), 7.60-7.57 (1H, m, Ar**H**), 7.51-7.46 (3H, m, Ar**H**), 7.45-7.37 (2H, m, Ar**H**), 4.44-4.37 (2H, m, C**H**$_2$CH$_3$), 1.32 (3H, t, *J* = 7.0 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 166.1 (d, *J* = 27.5 Hz, C), 160.4 (d, *J* = 25.0 Hz, C), 151.0 (C), 140.3 (C), 133.8 (d, *J* = 22.5 Hz, C), 129.8 (CH), 128.5 (2 x CH), 126.4 (CH), 125.9 (d, *J* = 8.0 Hz, 2 x CH), 124.9 (CH), 121.3 (CH), 111.2 (CH), 92.1 (d, *J* = 192.0 Hz, C), 63.3 (CH_2), 13.9 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ −152.2; HRMS (ES) Exact mass calcd for $C_{17}H_{15}FNO_3$ $[M+H]^+$: 300.1031, found: 300.1030; Enantiomeric excess was determined by HPLC with a Chiralpak IA-3 column (99:1 hexane:*i*-PrOH, 1.2 mL/min, 254 nm, 25 °C); t_r (major) = 11.1 min, t_r (minor) = 16.7 min; 75% *ee*.

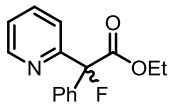
tert-Butyl 2-fluoro-2-(1-methyl-1H-1,3-benzodiazol-2-yl)propanoate 6.06



General procedure D was applied to **2.63** (13 mg, 49 μmol), [((*R*)-BINAP)Pd$(OH_2)_2]^{2+}2OTf^-$ (3 mg, 5 mol%) and NFSI (17 mg, 54 μmol) at 50 °C. The product was purified as described above (pet. ether/acetone 19:1) to give *2-fluoroazaarylacetate* **6.06** (19% conv.) as a white solid. R_f 0.38 (pet. ether/acetone 19:1); m.p. 92 °C; IR (film, cm^{-1}) 2980, 2934, 2857, 1753 (C=O), 1472, 1395, 1371, 1333, 1285, 1250; ^1H NMR (500 MHz, $CDCl_3$) δ 7.84 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.40-7.29 (3H, m, Ar**H**), 3.85 (3H, d, *J* = 1.5 Hz, NC**H**$_3$), 2.22 (3H, d, *J* = 22.5 Hz, CFC**H**$_3$), 1.45 (9H, s, C(C**H**$_3$)$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 168.0 (d, *J* = 28.5 Hz, C), 149.4 (d, *J* = 24.5 Hz, C), 141.5 (C), 136.5 (C), 123.7 (CH), 122.5 (CH), 120.5 (CH), 109.5 (CH), 92.2 (d, *J* = 181.5 Hz, C), 84.0 (C), 30.8 (d, *J* = 6.0 Hz, CH_3), 27.8 (3 x CH_3), 22.8 (d, *J* = 22.5 Hz, CH_3);^{19}F NMR (376 MHz, $CDCl_3$) δ −149.1; HRMS (ES) Exact mass calcd for $C_{15}H_{20}FN_2O_2$ $[M+H]^+$: 279.1503, found: 279.1503; Enantiomeric excess was determined by HPLC with a Chiralpak IA-3 column (99:1 hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C); t_r (minor) =

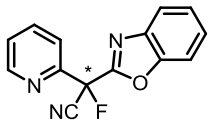
11.8 min, t_r (major) = 14.7 min; 10% *ee*.

Ethyl 2-fluoro-2-phenyl-2-(pyridin-2-yl)acetate 6.07



General procedure D was applied to **2.72** (12 mg, 50 μmol), [((*R*)-BINAP)Pd$(OH_2)_2]^{2+}2OTf^-$ (3 mg, 5 mol%) and NFSI (17 mg, 55 μmol) at room temperature. The product was purified as described above (pet. ether/EtOAc 9:1) to give *2-fluoroazaarylacetate* **6.07** (43% conv.) as a colourless oil. R_f 0.68 (pet. ether/EtOAc 2:1); IR (film, cm^{-1}) 3063, 2990, 1753 (C=O), 1589, 1493, 1468, 1449, 1435, 1300, 1256; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (1H, d, *J* = 4.5 Hz, Ar**H**), 7.73 (1H, dt, *J* = 8.0, 1.5 Hz, Ar**H**), 7.59-7.53 (2H, m, Ar**H**), 7.43-7.36 (4H, m, Ar**H**), 7.33-7.29 (1H, m, Ar**H**), 4.36 (2H, q, *J* = 7.0 Hz, $CO_2C\mathbf{H}_2CH_3$), 1.30 (3H, t, *J* 7.0 Hz, $CO_2CH_2C\mathbf{H}_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 168.8 (d, *J* = 26.5 Hz, C), 157.9 (d, *J* = 24.0 Hz, C), 149.1 (CH), 137.1 (d, *J* = 23.0 Hz, C), 136.9 (CH), 128.8 (CH), 128.1 (2 x CH), 126.6 (d, *J* = 8.0 Hz, 2 x CH), 123.7 (CH), 121.9 (d, *J* = 5.0 Hz, CH), 97.7 (d, *J* = 189.0 Hz, C), 62.4 (CH_2), 14.0 (CH_3); ^{19}F NMR (400 MHz, $CDCl_3$) δ −147.6; m/e (ES+): calc. for $C_{15}H_{15}FNO_2$ $[M+H]^+$ 260.1081, found 260.1080; Enantiomeric excess was determined by HPLC with a Chiralpak IA-3 column (99:1 hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C); t_r (major) = 10.1 min, t_r (minor) = 13.6 min; 6% *ee*.

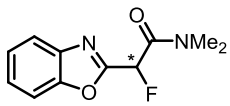
2-(1,3-Benzoxazol-2-yl)-2-fluoro-2-(pyridin-2-yl)acetonitrile 6.08



General procedure D was applied to **2.88** (12 mg, 49 μmol), [((*R*)-BINAP)Pd$(OH_2)_2]^{2+}2OTf^-$ (3 mg, 5 mol%) and NFSI (17 mg, 54 μmol) at −20 °C. The product was purified as described above (toluene/acetone 9:1) to give *fluorinated heterocycle* **6.08** (90% conv.) as a white solid. R_f (toluene/acetone 9:1) 0.72; m.p. 102 °C; IR (film, cm^{-1}) 1614, 1589, 1566, 1468, 1450, 1437, 1350, 1287, 1236, 1175; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.71-8.68 (1H, m, Ar**H**), 7.96 (1H, dt, *J* = 8.0, 1.5 Hz, Ar**H**), 7.87 (2H, dt, *J* = 8.0, 1.0 Hz, Ar**H**), 7.62-7.58 (1H, m, Ar**H**), 7.50-7.41 (3H, m, Ar**H**);

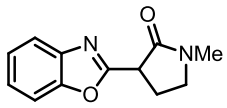
^{13}C NMR (125.8 MHz, $CDCl_3$) δ 157.0 (d, *J* = 26.5 Hz, C), 151.5 (C), 151.3 (C), 150.1 (d, *J* = 2.0 Hz, CH), 140.2 (C), 138.0 (CH), 127.2 (CH), 125.6 (CH), 125.6 (CH), 121.7 (CH), 120.5 (d, *J* = 5.0 Hz, CH), 113.6 (d, *J* = 32.5 Hz, C), 111.5 (CH), 86.2 (d, *J* = 190.0 Hz, C); ^{19}F NMR (376 MHz, $CDCl_3$) δ −145.0; HRMS (ES) Exact mass calcd for $C_{14}H_9FN_3O$ $[M+H]^+$: 254.0724, found: 254.0722; Enantiomeric excess was determined by HPLC with a Chiralpak IA-3 column (99:1 hexane:*i*-PrOH, 1.2 mL/min, 254 nm, 25 °C); t_r (minor) = 14.4 min, t_r (major) = 15.0 min; 12% *ee*.

2-(1,3-Benzoxazol-2-yl)-2-fluoro-*N*,*N*-dimethylacetamide 5.03



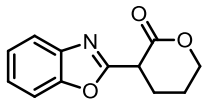
General procedure D was applied to **2.93** (10 mg, 49 μmol), [((*R*)-BINAP)Pd$(OH_2)_2$]$^{2+}$2OTf$^-$ (3 mg, 5 mol%) and NFSI (17 mg, 54 μmol) at –20°C. The product was purified as described above (pet. ether/EtOAc 1:1) to give *2-fluoroazaarylamide* **5.03** (56% conv.) as a yellow oil. R_f 0.21 (*n*-hexane/EtOAc 1:1); IR (film, cm^{-1}) 2926, 2855, 1680 (C=O), 1612, 1568, 1452, 1404, 1350, 1240, 1063; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81-7.79 (1H, m, Ar**H**), 7.62-7.60 (1H, m, Ar**H**), 7.46-7.39 (2H, m, Ar**H**), 6.34 (1H, d, *J* = 47.3 Hz, C**H**F), 3.15 (3H, d, *J* = 1.8 Hz, NC**H**$_3$), 3.08 (3H, d, *J* = 0.6 Hz, NC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 163.6 (d, *J* = 21.8 Hz, C), 158.0 (d, *J* = 23.2 Hz, C) , 151.0 (C), 140.4 (C), 126.4 (CH), 125.0 (CH), 120.9 (CH), 111.3 (CH), 83.9 (d, *J* = 188.2 Hz, CH), 36.7 (d, *J* = 5.3 Hz, CH_3), 36.4 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ −184.0; HRMS (ES) Exact mass calcd for $C_{11}H_{12}FN_2O_2$ $[M+H]^+$: 223.0877, found: 223.0878; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10 hexane:*i*-PrOH, 0.8 mL/min, 254 nm, 25 °C); t_r (minor) = 17.5 min; t_r (major) = 19.6 min; 86% *ee*.

3-(1,3-Benzoxazol-2-yl)-1-methylpyrrolidin-2-one 2.97



General procedure A was applied to 2-chlorobenzoxazole (0.74 mL, 6.5 mmol), *N*-Methyl-2-pyrrolidone (0.63 mL, 6.5 mmol) and NaHMDS (0.6 M in toluene, 21.7 mL, 13.0 mmol). The reaction was stirred for 2 h and purified by flash chromatography (CH_2Cl_2→CH_2Cl_2/MeOH 99:1) to give *azaarylamide* **2.97** (738 mg, 52%) as a brown solid. R_f 0.19 (CH_2Cl_2/MeOH 98:2); m.p. 76 °C; IR (film, cm^{-1}) 3059, 2951, 2882, 2245, 1694 (C=O), 1612, 1566, 1499, 1454, 1433; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71-7.66 (1H, m, Ar**H**), 7.53-7.48 (1H, m, Ar**H**), 7.33-7.27 (2H, m, Ar**H**), 4.06 (1H, dd, *J* = 9.0, 8.0 Hz, $CON(CH_3)CH_2CH_2C\mathbf{H}$), 3.65-3.60 (1H, m, $CON(CH_3)C\mathbf{H}_aH_bCH_2CH$), 3.51-3.45 (1H, m, $CON(CH_3)CH_a\mathbf{H}_bCH_2CH$), 2.93 (3H, s, $CON(C\mathbf{H}_3)CH_2CH_2CH$), 2.71-2.62 (1H, m, $CON(CH_3)CH_2C\mathbf{H}_aH_bCH$), 2.60-2.50 (1H, m, $CON(CH_3)CH_2CH_a\mathbf{H}_bCH$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 169.9 (C), 163.7 (C), 151.0 (C), 140.9 (C), 124.9 (CH), 124.3 (CH), 119.8 (CH), 110.7 (CH), 47.6 (CH_2), 42.7 (CH), 30.1 (CH_3), 23.7 (CH_2); HRMS (ES) Exact mass calcd for $C_{12}H_{13}N_2O_2$ $[M+H]^+$: 217.0972, found: 217.0973.

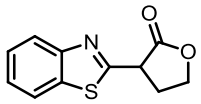
3-(1,3-Benzoxazol-2-yl)oxan-2-one 2.98[126]



General procedure A was applied to 2-chlorobenzoxazole (0.74 mL, 6.5 mmol), δ-valerolactone (0.60 mL, 6.5 mmol) and NaHMDS (0.6 M in toluene, 21.7 mL, 13.0 mmol). The reaction was stirred for 1 h and purified by flash chromatography (pet. ether/EtOAc 3:1→1:2) and recrystallised (EtOAc/*n*-hexane) to give azaarylacetate **2.98** (351 mg, 25%) as a white powder. R_f 0.42 (pet. ether/EtOAc 1:1); m.p. 90 °C; ^{1}H NMR (400 MHz, CD_3CN) δ 7.71-7.69 (1H, m, Ar**H**), 7.62-7.58 (1H, m, Ar**H**), 7.42-7.35 (2H, m, Ar**H**), 4.51-4.42 (2H, m, $CO_2C\mathbf{H}_2CH_2CH_2CH$), 4.32 (1H, dd, *J* = 9.5, 8.5 Hz, $CO_2CH_2CH_2CH_2C\mathbf{H}$), 2.47-2.39 (2H, m, $CO_2CH_2CH_2C\mathbf{H}_2CH$), 2.12-1.99 (2H, m $CO_2CH_2C\mathbf{H}_2CH_2CH$); ^{13}C NMR (125.8 MHz, CD_3CN) δ 169.8 (C), 164.4 (C), 151.8 (C), 141.9 (C), 126.3 (CH), 125.5 (CH), 120.7 (CH), 111.6 (CH), 70.4 (CH), 42.3 (CH_2),

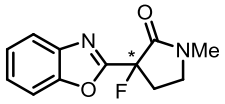
24.3 (CH_2), 21.8 (CH_2). Data consistent with literature.[126]

3-(1,3-Benzothiazol-2-yl)oxolan-2-one 2.99



General procedure A was applied to 2-chlorobenzothiazole (80 μL, 0.59 mmol), γ-butyrolactone (50 μL, 0.59 mmol) and NaHMDS (0.6 M in toluene, 1.97 mL, 1.18 mmol). The reaction was stirred for 3 h and purified by flash chromatography (pet. ether/Et_2O 3:1→1:1) to give *azaarylacetate* **2.99** (47 mg, 36%) as a yellow solid. R_f 0.21 (pet. ether/EtOAc 1:1); m.p. 124 °C (decomp.); IR (film, cm^{-1}) 3063, 2913, 1767 (C=O), 1593, 1510, 1456, 1435, 1375, 1314, 1219; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.90-7.87 (1H, m, Ar**H**), 7.51-7.47 (1H, m, Ar**H**), 7.42-7.38 (1H, m, Ar**H**), 4.65-4.60 (1H, m, $CO_2C\mathbf{H}_aH_bCH_2CH$), 4.49-4.43 (1H, m, $CO_2CH_a\mathbf{H}_bCH_2CH$), 4.28 (1H, t, *J* = 9.0 Hz, $CO_2CH_2CH_2C\mathbf{H}$), 3.00 (1H, dq, *J* = 13.0, 9.0 Hz, $CO_2CH_2C\mathbf{H}_aH_bCH$), 2.87 (1H, dddd, *J* = 13.0, 9.0, 7.0, 4.5 Hz, $CO_2CH_2CH_a\mathbf{H}_bCH$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 174.2 (C), 164.6 (C), 152.5 (C), 135.4 (C), 126.2 (CH), 125.4 (CH), 123.0 (CH), 121.6 (CH), 67.4 (CH_2), 44.6 (CH), 29.0 (CH_2); HRMS (ES) Exact mass calcd for $C_{11}H_{10}NO_2S$ $[M+H]^+$: 220.0427, found: 220.0424.

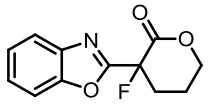
3-(1,3-Benzoxazol-2-yl)-3-fluoro-1-methylpyrrolidin-2-one 6.09



General procedure D was applied to **2.97** (10 mg, 49 μmol), $[((R)\text{-BINAP})Pd(OH_2)_2]^{2+}2OTf^-$ (3 mg, 5 mol%) and NFSI (17 mg, 54 μmol) at −20 °C. The product was purified as described above ($CHCl_3$/EtOAc 19:1→9:1) to give *2-fluoroazaarylamide* **6.09** (14% conv.) as a brown solid. R_f 0.24 ($CHCl_3$/EtOAc 9:1); m.p. 80 °C; IR (film, cm^{-1}) 2889, 2247, 1717 (C=O), 1612, 1564, 1499, 1476, 1452, 1406, 1350; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78-7.75 (1H, m, Ar**H**), 7.64-7.61 (1H, m, Ar**H**), 7.44-7.36 (2H, m, Ar**H**), 3.67-3.58 (2H, m, $CON(CH_3)C\mathbf{H}_2CH_2CF$), 3.26 (1H, ddt, *J* = 14.5, 7.5, 4.0 Hz, $CON(CH_3)CH_2C\mathbf{H}_aH_bCF$), 3.00 (3H, d, *J* = 1.0 Hz, $NC\mathbf{H}_3$), 2.71 (1H, dddd, *J* = 22.5, 14.5, 8.5, 6.5 Hz, $CON(CH_3)CH_2CH_a\mathbf{H}_bCF$); ^{13}C NMR (125.8 MHz, $CDCl_3$)

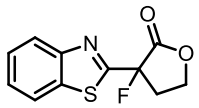
δ 166.2 (d, *J* = 25.0 Hz, C), 160.0 (d, *J* = 29.0 Hz, C), 151.4 (C), 140.3 (C), 126.1 (CH), 124.9 (CH), 120.6 (CH), 111.5 (CH), 92.3 (d, *J* = 189.5 Hz, C), 45.2 (d, *J* = 3.0 Hz, CH_2), 30.8 (d, *J* = 21.0 Hz, CH_2), 30.6 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ −157.9; HRMS (ES) Exact mass calcd for $C_{12}H_{11}FN_2O_2Na$ $[M+Na]^+$: 257.0697, found: 257.0690; Enantiomeric excess was determined by HPLC with a Chiralpak IA-3 column (85:15 hexane:EtOH, 1.0 mL/min, 230 nm, 25 °C); t_r (major) = 13.0 min, t_r (minor) = 17.1 min; 66% *ee*.

3-(1,3-Benzoxazol-2-yl)-3-fluorooxan-2-one 6.10



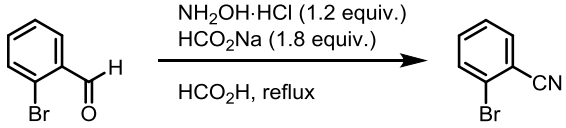
General procedure D was applied to **2.98** (10 mg, 49 μmol), $[((R)\text{-BINAP})Pd(OH_2)_2]^{2+}2OTf^-$ (3 mg, 5 mol%) and NFSI (17 mg, 54 μmol). The product was purified as described above (pet. ether/Et_2O 2:1→1:2) to give *2-fluoroazaarylacetate* **6.10** (48% conv.) as a colourless oil. R_f 0.35 (pet. ether/Et_2O 1:2); IR (film, cm^{-1}) 2986, 1763 (C=O), 1736, 1616, 1576, 1551, 1477, 1454, 1406, 1369; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83-7.79 (1H, m, Ar**H**), 7.65-7.61 (1H, m, Ar**H**), 7.49-7.39 (2H, m, Ar**H**), 4.54 (1H, ddd, *J* = 12.0, 6.5, 5.5 Hz, $CO_2C\mathbf{H}_aH_bCH_2CH_2CF$), 4.45 (1H, *J* = 12.0, 6.5, 5.5 Hz, $CO_2CH_aH_bCH_2CH_2CF$), 3.19 (1H, ddd, *J* = 21.0, 7.5, 7.0 Hz, $CO_2CH_2CH_2C\mathbf{H}_aH_bCF$), 2.65-2.52 (1H, m, $CO_2CH_2CH_2CH_a\mathbf{H}_bCF$), 2.29-2.13 (2H, m, $CO_2CH_2C\mathbf{H}_2CH_2CF$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 164.6 (d, *J* = 24.5 Hz, C), 159.3 (d, *J* = 26.0 Hz, C), 151.1 (C), 140.1 (C), 126.7 (CH), 125.2 (CH), 121.0 (CH), 111.5 (CH), 88.2 (d, *J* = 189.0 Hz, C), 69.5 (CH_2), 30.2 (d, *J* = 22.5 Hz, CH_2), 20.2 (d, *J* = 5.5 Hz, CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ −147.2; LRMS (GCMS) $[M]^+$: 235.1; Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (90:10 hexane:*i*-PrOH, 0.8 mL/min, 254 nm, 25 °C); t_r (minor) = 18.4 min, t_r (major) = 20.3 min; 58% *ee*.

3-(1,3-Benzothiazol-2-yl)-3-fluorooxolan-2-one 6.11



General procedure D was applied to **2.99** (11 mg, 49 μmol), $[((R)\text{-BINAP})Pd(OH_2)_2]^{2+}2OTf^-$ (3 mg, 5 mol%) and NFSI (17 mg, 54 μmol) at room temperature. The product was purified as described above (pet. ether/EtOAc 3:1→2:1) to give *2-fluoroazaarylacetate* **6.11** (50% conv.) as an orange solid. R_f 0.63 (pet. ether/EtOAc 2:1); m.p. 114 °C; IR (film, cm^{-1}) 3059, 3026, 2924, 2853, 1794 (C=O), 1726, 1599, 1493, 1452, 1377; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07-8.05 (1H, m, Ar**H**), 7.99-7.96 (1H, m, Ar**H**), 7.55 (1H, ddd, *J* = 8.5, 7.5, 1.5 Hz, Ar**H**), 7.48 (1H, ddd, *J* = 8.5, 7.5, 1.0 Hz, Ar**H**), 4.80-4.74 (1H, m, $CO_2CH_aH_bCH_2CF$), 4.67 (1H, dt, *J* = 9.0, 4.0 Hz, $CO_2CH_a\mathbf{H}_bCH_2CF$), 3.41 (1H, ddt, *J* = 14.0, 7.0, 4.0 Hz, $CO_2CH_2CH_aH_bCF$), 3.04-2.92 (1H, m, $CO_2CH_2CH_a\mathbf{H}_bCF$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 169.7 (d, *J* = 26.0 Hz, C), 164.7 (*J* = 34.0 Hz, C), 152.5 (C), 135.5 (C), 126.6 (CH), 126.2 (CH), 123.8 (CH), 122.0 (CH), 93.6 (d, *J* = 189.5 Hz, C), 65.5 (d, *J* = 4.5 Hz, CH_2), 34.8 (d, *J* = 20.5 Hz, CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ −151.0; HRMS (ES) Exact mass calcd for $C_{11}H_9FNO_2$ $[M+H]^+$: 238.0333, found: 238.0332; Enantiomeric excess was determined by HPLC with a Chiralpak IA-3 column (98:2 hexane:*i*-PrOH, 1.0 mL/min, 230 nm, 25 °C); t_r (major) = 14.9 min, t_r (minor) = 16.1 min; 10% *ee*.

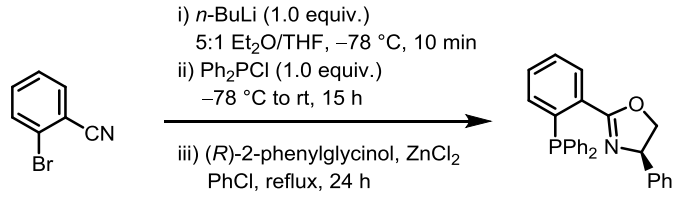
2-Bromobenzonitrile 6.12[326]



To a stirred solution of hydroxylamine hydrochloride (218 mg, 3.13 mmol) and sodium formate (340 mg, 5.00 mmol) in formic acid (5 mL) was added 2-bromobenzaldehyde (0.32 mL, 2.70 mmol). The reaction was heated for 4 h at reflux, cooled to room temperature and water added (5 mL). The phases were separated and the aqueous phase extracted with EtOAc (3 x 5 mL). The combined organics were concentrated *in vacuo* to remove formic acid. The residue was dissolved in Et_2O (10 mL), washed with water (10 mL) and brine

(10 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* to give crude nitrile. The product was purified by flash chromatography (pet. ether/Et_2O 19:1→9:1) to give nitrile **6.12** (420 mg, 85%) as a colourless solid. R_f 0.56 (pet. ether/Et_2O 3:1); m.p. 46 °C (lit. 53-54 °C)[327]; ^1H NMR (500 MHz, $CDCl_3$) δ 7.68-7.61 (2H, m, Ar**H**), 7.49-7.39 (2H, m, Ar**H**); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 134.1 (CH), 133.8 (CH), 133.0 (CH), 127.5 (CH), 125.0 (C), 117.0 (C), 115.5 (C). Data consistent with literature.[326]

(4*R*)-2-[2-(Diphenylphosphanyl)phenyl]-4-phenyl-4,5-dihydro-1,3-oxazole (*R*)-Ph-PHOX[328]



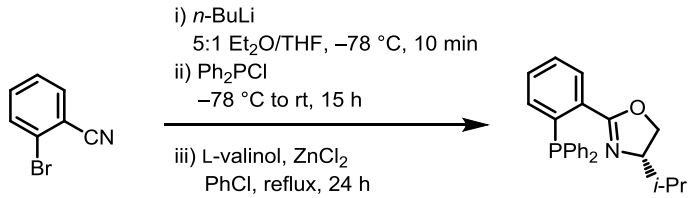
6.12 (*R*)-Ph-PHOX
48% over 2 steps

To a stirred solution of 2-bromobenzonitrile **6.12** (590 mg, 3.24 mmol) in 5:1 Et_2O/THF (20 mL) at −78 °C under nitrogen was added *n*-BuLi (1.6 M in hexanes, 2.03 mL, 3.24 mmol). The reaction was stirred for 10 min and a solution of (chloro)diphenylphosphine (0.59 mL, 3.24 mmol) in THF (4 mL) was added dropwise. The reaction was stirred at −78 °C for 3 h and allowed to warm to room temperature for 16 h. The red-brown suspension was quenched with water (15 mL), the phases separated and the aqueous phase extracted with Et_2O (3 x 15 mL). The combined organics were dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was recrystallised (*i*-PrOH) to give 2-(diphenylphosphanyl)benzonitrile as pale yellow crystals (543 mg, 58%).

A stirred suspension of 2-(diphenylphosphanyl)benzonitrile (250 mg, 0.870 mmol), (*R*)-2-phenylgylcinol (155 mg, 1.13 mmol) and $ZnCl_2$ (285 mg, 2.09 mmol) in chlorobenzene (20 mL) was heated at reflux for 24 h. The reaction was cooled to room temperature and quenched with sat. aq. NH_4Cl solution (20 mL). The phases were separated and the aqueous phase extracted with CH_2Cl_2 (3 x 20 mL). The combined organics were

dried (Na_2SO_4) and the solvent removed *in vacuo*. The product was purified by flash chromatography (pet. ether/CH_2Cl_2 1:1 followed by pet. ether/EtOAc 3:1) to give **(*R*)-Ph-PHOX** (289 mg, 82%) as a cream gel. R_f 0.50 (pet. ether/EtOAc 3:1); $[\alpha]_D^{25}$ −11.9 (*c* 1.00, $CHCl_3$) (lit. −28.1 (*c* 1.43, $CHCl_3$))[328]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (1H, ddd, *J* = 7.5, 3.5, 1.5 Hz, Ar**H**), 7.44-7.32 (12H, m, Ar**H**), 7.25-7.22 (3H, m, Ar**H**), 6.99-6.94 (3H, m, Ar**H**), 5.27 (1H, t, *J* = 9.5 Hz, C**H**Ph), 4.59 (1H, dd, *J* = 10.0 Hz, 8.5 Hz, C**H**$_a$CHO), 3.98 (1H, dd, *J* = 9.0, 8.5 Hz, CH$_a$C**H**$_b$O); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 164.6 (d, $^3J_{C\text{-}P}$ = 2.5 Hz, C), 141.9 (C), 139.1 (d, $^2J_{C\text{-}P}$ = 26.0 Hz, C), 138.0 (d, $^1J_{C\text{-}P}$ = 12.5 Hz, C), 137.8 (d, $^1J_{C\text{-}P}$ = 12.5 Hz, C), 134.3 (d, *J* = 21.0 Hz, 2 x CH), 133.8 (d, *J* = 21.0 Hz, 2 x CH), 133.8 (d, *J* = 1.0 Hz, CH), 131.4 (d, $^1J_{C\text{-}P}$ = 19.0 Hz, C), 130.6 (CH), 130.2 (d, $^3J_{C\text{-}P}$ = 3.0 Hz, CH), 128.6-128.3(8 x CH), 128.0 (CH), 127.1 (CH), 126.6 (2 x CH), 74.3 (CH_2), 70.0 (CH); ^{31}P NMR (162 MHz, $CDCl_3$) δ −5.4. Data consistent with literature.[328]

(4*S*)-2-[2-(Diphenylphosphanyl)phenyl]-4-(propan-2-yl)-4,5-dihydro-1,3-oxazole (*S*)-*i*-Pr-PHOX[329]

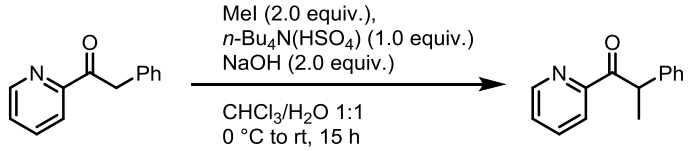


6.12 **(*S*)-*i*-Pr-PHOX** 44% over 2 steps

A stirred suspension of 2-(diphenylphosphanyl)benzonitrile (200 mg, 0.696 mmol), (*S*) 2-amino-3-methyl-1-butanol (93 mg, 0.91 mmol) and $ZnCl_2$ (228 mg, 1.67 mmol) in chlorobenzene (10 mL) was heated at reflux for 48 h. The reaction was cooled to room temperature and quenched with sat. aq. NH_4Cl solution (10 mL). The phases were separated and the aqueous phase extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were dried (Na_2SO_4) and the solvent removed *in vacuo*. The product was purified by flash chromatography (pet. ether/CH_2Cl_2 1:1 followed by pet. ether/EtOAc 3:1) to give **(*S*)-*i*-Pr-PHOX** (194 mg, 75%) as a colourless solid. R_f (0.86 pet/ ether/EtOAc 3:1); m.p.

78 °C (lit. 57-58 °C)[329]; $[\alpha]_D^{25}$ −29.0 (*c* 0.97, $CHCl_3$) (lit. −40 (*c* 0.5, $CHCl_3$))[329]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (1H, ddd, *J* = 7.5, 3.5, 1.5 Hz, Ar**H**), 7.39-7.25 (12H, m, Ar**H**), 6.90 (1H, ddd, *J* = 8.0, 4.0, 1.0 Hz, Ar**H**), 4.20-4.11 (1H, m, C**H**$_a$H$_b$O), 3.92-3.83 (2H, m, CH$_a$**H**$_b$O and C**H**N), 1.56-1.46 (1H, m, C**H**(CH$_3$)$_3$), 0.84 (3H, d, *J* = 6.5 Hz, C**H**$_3$), 0.73 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 162.9 (d, $^3J_{C\text{-}P}$ = 2.5 Hz, C), 138.8 (d, $^2J_{C\text{-}P}$ = 25.5 Hz, C), 138.2 (d, $^1J_{C\text{-}P}$ = 12.5 Hz, C), 138.0 (d, $^1J_{C\text{-}P}$ = 10.0 Hz, C), 134.2 (d, $^2J_{C\text{-}P}$ = 21.0 Hz, 2 x CH), 133.8 (d, $^3J_{C\text{-}P}$ = 1.0 Hz, CH) , 133.7 (d, $^2J_{C\text{-}P}$ = 20.5 Hz, 2 x CH), 131.9 (d, $^1J_{C\text{-}P}$ = 19.0 Hz, C), 130.3 (CH), 129.8 (d, $^3J_{C\text{-}P}$ = 3.0 Hz, CH), 128.5-128.2 (6 x CH), 127.9 (CH), 73.1 (CH), 70.0 (CH_2), 32.7 (CH), 18.8 (CH_3), 18.3 (CH_3); ^{31}P NMR (162 MHz, $CDCl_3$) δ −5.5. Data consistent with literature.[329]

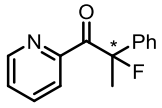
2-Phenyl-1-(pyridin-2-yl)propan-1-one 2.103[135]



To a stirred solution of pyridyl ketone **2.102** (750 mg, 3.80 mmol), methyl iodide (0.47 mL, 7.6 mmol) and tetrabutylammonium hydrogen sulphate (1.29 mg, 3.80 mmol) in chloroform (7.5 mL) at 0 °C was added sodium hydroxide (304 mg, 7.61 mmol) in water (7.5 mL). The reaction was warmed to room temperature for 16 h and diluted with $CHCl_3$/H_2O 1:1 (15 mL). The phases were separated and the aqueous phase extracted with $CHCl_3$ (3 x 15 mL). The combined organics were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was treated with Et_2O (10 mL) and filtered. The filtrate was concentrated *in vacuo* and the crude product was purified by flash chromatography on alumina (pet. ether/Et_2O 19:1→4:1) to give methylated pyridyl ketone **2.103** (576 mg, 72%) as a colourless solid. R_f 0.69 (pet. ether/EtOAc 4:1); m. p. 54 °C (lit. 64.5-65 °C)[135]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69-8.65 (1H, m, Ar**H**),8.03-8.00 (1H, m, Ar**H**), 7.77 (1H, dt, *J* = 8.0, 1.5 Hz, Ar**H**), 7.42-7.37 (3H,

m, Ar**H**), 7.30-7.24 (2H, m, Ar**H**), 7.20-7.15 (1H, m, Ar**H**), 5.49 (1H, q, *J* = 7.0 Hz, C**H**CH_3), 1.57 (3H, d, *J* = 7.0 Hz, CHC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 201.8 (C), 152.9 (C), 148.8 (CH), 140.9 (C), 136.8 (CH), 128.5 (2 x CH), 128.4 (2 x CH), 126.9 (CH), 126.6 (CH), 122.8 (CH), 44.9 (CH), 18.2 (CH_3). Data consistent with literature.[135]

2-Fluoro-2-phenyl-1-(pyridin-2-yl)propan-1-one 2.104

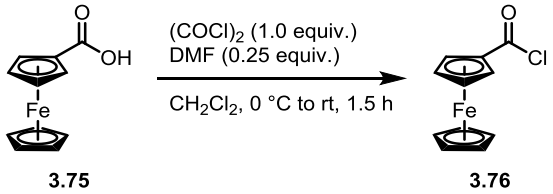


General procedure D was applied to **2.103** (11 mg, 50 μmol), [((*R*)-BINAP)Pd$(OH_2)_2]^{2+}2OTf^-$ (3 mg, 5 mol%) and NFSI (17 mg, 55 μmol) at room temperature in CH_2Cl_2. The product was purified as described above (pet. ether/EtOAc 19:1→9:1) to give *2-fluoroazaarylketone* **2.104** (25% conv.) as a white solid. R_f 0.29 (pet. ether/EtOAc 9:1); IR (film, cm^{-1}) 1709 (C=O), 1582, 1495, 1447, 1371, 1281, 1240, 997, 968, 910; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62-8.57 (1H, m, Ar**H**), 7.96-7.93 (1H, m, Ar**H**), 7.75 (1H, dt, *J* = 8.0, 1.5 Hz, Ar**H**), 7.60-7.56 (2H, m, Ar**H**), 7.39-7.34 (3H, m, Ar**H**), 7.33-7.28 (m, 1 H, Ar**H**), 2.20 (3H, d, *J* = 23.5 Hz, C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 196.6 (d, $^2J_{C\text{-}F}$ = 25.0 Hz, C), 151.7 (d, *J* = 1.0 Hz, C), 148.8 (CH), 139.4 (d, $^2J_{C\text{-}F}$ = 22.0 Hz, C), 136.5 (CH), 128.4 (2 x CH), 128.3 (d, *J* = 1.5 Hz, CH), 126.6 (CH), 125.4 (d, $^3J_{C\text{-}F}$ = 7.5 Hz, 2 x CH), 124.7 (d, *J* = 4.0 Hz, CH), 99.9 (d, *J* = 183.0 Hz, C), 24.9 (d, *J* = 24.0 Hz, CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ −143.5; HRMS (ES) Exact mass calcd for $C_{14}H_{13}FNO$ $[M+H]^+$: 230.0903, found: 230.0904. Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (98:2 hexane:*i*-PrOH, 0.8 mL/min, 230 nm, 25 °C); t_r (minor) = 13.5 min, t_r (major) = 15.0 min; 37% *ee*.

6.3 Oxidative Annulation of Ferrocene Derivatives

6.3.1 General Procedures

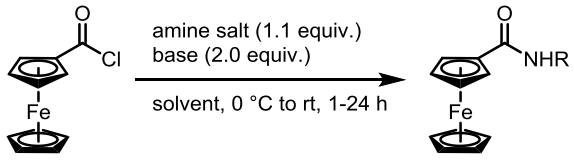
General Procedure A: Synthesis of ferrocenecarboxylic acid chloride 3.76



3.75 **3.76**

To a stirred solution of ferrocenecarboxylic acid **3.75** (1.0 equiv.) and DMF (0.25 equiv.) in anhydrous CH_2Cl_2 (0.55 M) at 0 °C under nitrogen was added oxalyl chloride (1.2 equiv.) dropwise. The reaction was stirred for 1 h at 0 °C and at room temperature for 30 min. The solvent was removed *in vacuo*. The residue was dissolved in warm hexane, decanted and the solvent removed *in vacuo* to give ferrocenecarboxylic acid chloride **3.76** that was used in the next step without further purification.

General Procedure B: Synthesis of ferrocenecarboxamides from ferrocenecarboxylic acid chloride 3.76



3.76

Method 1

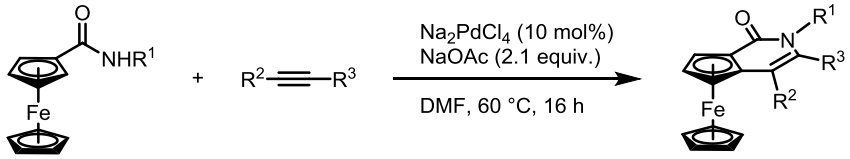
To a biphasic mixture of base (2.0 equiv.) in a 2:1 mixture of EtOAc/H_2O (0.2 M) was added amine salt (1.1 equiv.). The solution was cooled to 0 °C and ferrocenecarboxylic acid chloride **3.76** (1.0 equiv.) added. The reaction was stirred for 1 h, warmed to room temperature and the phases separated. The aqueous phase was extracted with EtOAc, the combined organics dried ($MgSO_4$) and the solvent removed *in vacuo*.

Method 2

To a stirred solution of amine (1.0-2.0 equiv.) and base (1.0-6.0 equiv.) in anhydrous CH_2Cl_2 (1 M) at 0 °C was added ferrocenecarboxylic acid **3.76** (1.0-1.1 equiv.). The reaction was

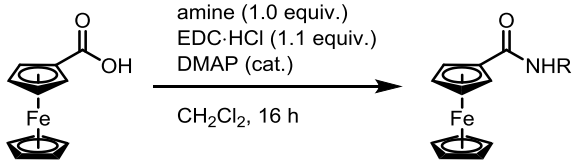
stirred for 4-24 h and quenched with 1 N aq. HCl (10 mL). The phases were separated and the aqueous phase extracted with CH_2Cl_2 (2 x 10 mL). The combined organics were dried ($MgSO_4$) and the solvent removed *in vacuo.*

General Procedure C: Oxidative Annulation



A solution of ferrocenecarboxamide (1.0 equiv.), sodium tetrachloropalladate (10 mol%), sodium acetate (2.1 equiv.) and alkyne (1.1 equiv.) in DMF (0.2 M) at 60 °C was stirred for 16 h. The reaction was passed through a plug of silica (with EtOAc/CH_2Cl_2 9:1 as eluent) and washed with brine/H_2O 1:1. The organic phase was dried ($MgSO_4$) and the solvent removed *in vacuo*.

General Procedure D: Synthesis of ferrocenecarboxamides from ferrocenecarboxylic acid 3.76

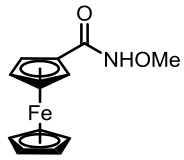


3.76

To a stirred solution of ferrocencecarboxylic acid **3.76** (200 mg, 0.869 mmol) and amine (0.790 mmol) in anhydrous CH_2Cl_2 (0.1 M) was added EDC·HCl (167 mg, 0.869 mmol) and DMAP (cat., 1 crystal). The reaction was stirred for 16 h, diluted with CH_2Cl_2 and washed with sat. aq. Na_2CO_3 and brine. The organic phase was dried (Na_2SO_4) and concentrated *in vacuo*.

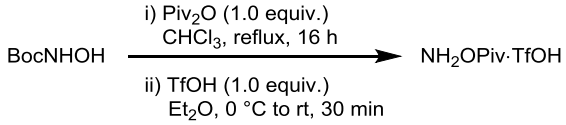
6.3.2 Data

_N_-Methoxyferrocenecarboxamide 3.77



General procedure B (method 1) was applied to K_2CO_3 (2.14 g, 15.5 mmol), methoxyamine hydrochloride (713 mg, 8.53 mmol) and ferrocenecarboxylic acid chloride **3.76** (1.77 g, 7.12 mmol) in EtOAc/H_2O 2:1 (36 mL). The residue was purified by flash chromatography (EtOAc/pet. ether 2:1→5:1) to give *N-methoxy amide* **3.77** (1.62 g, 88%) as an orange powder. R_f 0.24 (pet. ether/EtOAc 1:1); m.p. 124 °C (decomp.); IR (film, cm^{-1}) 3177, 3013, 2932, 2361, 1626 (C=O), 1522, 1439, 1377, 1302, 1225; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (1H, br s, N**H**), 4.72 (2H, s, Ar**H**), 4.40 (2H, s, Ar**H**), 4.25 (5H, s, Ar**H**), 3.86 (3H, s, OC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 170.2 (C), 72.6 (C), 70.8 (2 x CH), 70.0 (5 x CH), 68.2 (2 x CH), 64.7 (CH_3); HRMS (ES) Exact mass calcd for $C_{12}H_{14}FeNO_2$ $[M+H]^+$: 260.0368, found: 260.0372.

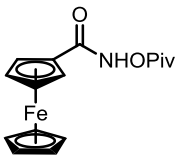
Amino 2,2-dimethylpropanoate 6.13[185]



To amino alcohol (3.20 g, 24.0 mmol) in chloroform (40 mL) was added pivalic anhydride (4.88 mL, 24.0 mmol). The reaction was heated at reflux for 16 h, cooled to room temperature and quenched with sat. aq. $NaHCO_3$ (40 mL). The phases were separated and the organic phase washed with sat. aq. $NaHCO_3$ (3 x 40 mL). The organic phase was dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give pivaloxy Boc-protected amine (4.72 g, 97%) as a colourless solid which was used in the next step without further purification. To pivaloxy Boc-protected amine (2.26 g, 11.1 mmol) in anhydrous Et_2O (30 mL) at 0 °C under nitrogen was added triflic acid (0.99 mL, 11.1 mmol). The reaction was warmed to room temperature over 30 min and diluted with hexane to precipitate the product. The product was filtered with hexane to give pivaloxy deprotected amine **6.13** (2.44 g, 82%) as a colourless solid. R_f 0.50 (pet. ether/EtOAc 2:1); m.p. 124-125 °C;

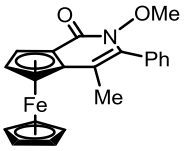
^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 1.11 (9H, s, C(C**H**$_3$)$_3$); ^{13}C NMR (125.8 MHz, $(CD_3)_2SO$) δ 179.431, 120.7 (C, q, $^{1}J_{C\text{-}F}$ = 323.0 Hz), 37.7 (C), 27.0 (3 x CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ −78.6. Data consistent with literature.[185]

Ferrocenecarboxamido 2,2-dimethylpropanoate 3.78



General procedure B (method 1) was added to Na_2CO_3 (1.02 g, 9.58 mmol), $NH_2OPiv{\cdot}TfOH$ **6.13** (1.28 g, 4.79 mmol) and ferrocenecarboxylic acid chloride **3.76** (1.09 g, 4.38 mmol) in EtOAc/H_2O 2:1 (21 mL). The residue was purified by recrystallisation (hexane/EtOAc) to give *pivaloxy amide* **3.78** as a fine orange powder (617 mg, 43%). R_f 0.79 (pet. ether/EtOAc 2:1); m.p. 138 °C (decomp.); IR (film, cm^{-1}) 2974, 1784 (C=O), 1651 (C=O), 1514, 1477, 1412, 1379, 1292, 1223, 1078; ^{1}H NMR (400 MHz, CD_3SO) δ 11.52 (1H, s, N**H**), 4.79-4.75 (2H, m, Ar**H**), 4.45-4.40 (2H, m, Ar**H**), 4.28 (5H, s, Ar**H**), 1.28 (9H, s, C(C**H**$_3$)$_3$); ^{13}C NMR (125.8 MHz, CD_3SO) δ 176.0 (C), 168.1 (C), 72.3 (C), 70.5 (2 x CH), 69.7 (5 x CH), 68.2 (2 x CH), 37.8 (C), 26.9 (3 x CH_3); HRMS (EI) Exact mass calcd for $C_{16}H_{19}FeNO_3$ $[M]^+$: 329.0709, found: 329.0705.

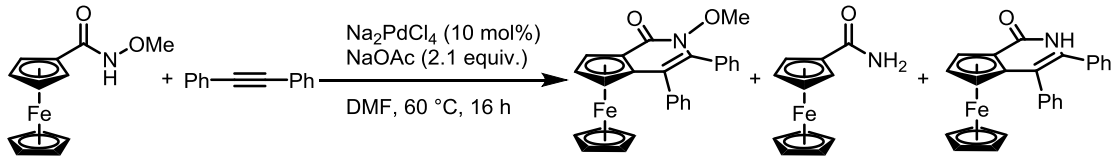
2-Methoxy-4-methyl-3-phenyl-1*H*-2*H*-ferrocenyl[1,2-*a*]pyridin-1-one 3.79



General procedure C was applied to ferrocenecarboxamide **3.77** (78 mg, 0.30 mmol), sodium tetrachloropalladate (9 mg, 10 mol%), sodium acetate (52 mg, 0.63 mmol) and 1-phenyl-1-propyne (41 μL, 0.33 mmol). The residue was purified by flash chromatography (pet. ether/EtOAc 4:1→1:2) to give *pyridinone* **3.79** (17 mg, 15%) as an orange oil. R_f 0.47 (pet. ether/EtOAc 1:1); IR (film, cm^{-1}) 3088, 2930, 2857, 2241, 1713, 1667 (C=O), 1616, 1595, 1555, 1495; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56-7.40 (3H, m, Ar**H**), 7.40-7.30 (2H, m, Ar**H**), 5.28-5.25 (1H, m, Ar**H**), 4.76-4.73 (1H, m, Ar**H**), 4.37 (1H, t, *J* = 2.5 Hz, Ar**H**), 4.09 (5H, s, Ar**H**), 3.61 (3H, s, OC**H**$_3$), 2.00 (3H, s, CC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 164.2 (C), 135.4 (C), 132.6 (C), 130.4 (CH), 130.3 (CH), 128.4 (2 x CH), 128.0 (CH), 111.7 (C), 88.1 (C),

73.1 (C), 71.4 (CH), 69.7 (5 x CH), 66.3 (CH), 64.3 (CH), 63.0 (CH), 14.8 (CH_3); HRMS (ES) Exact mass calcd for $C_{21}H_{20}FeNO_2$ $[M+H]^+$: 374.0838, found: 374.0839.

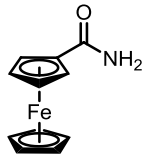
3,4-Diphenyl-1*H*,2*H*-ferrocenyl[1,2-*a*]pyridin-1-one 3.91



3.77 **3.87** **3.91** 20% **3.89** 20% **3.92** 4%

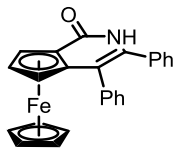
General procedure C was applied to ferrocenecarboxamide **3.77** (78 mg, 0.30 mmol), sodium tetrachloropalladate (9 mg, 10 mol%), sodium acetate (52 mg, 0.63 mmol) and diphenylacetylene (59 mg, 0.33 mmol). The residue was purified by flash chromatography (pet. ether/EtOAc 4:1→2:1) to give *pyridinone* **3.91** (26 mg, 20%) as an orange solid, ferrocenecarboxamide **3.89** (14 mg, 20%) as a yellow solid and *pyridinone* **3.92** (5 mg, 4%) as an orange oil. R_f 0.54 (pet. ether/EtOAc 1:1); m.p. 88 °C (decomp.); IR (film, cm^{-1}) 3109, 2934, 2851, 2245, 1667 (C=O), 1589, 1493, 1443, 1302, 1227; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27-7.16 (10H, m, Ar**H**), 5.32 (1H, dd, *J* = 2.5, 1.5 Hz, Ar**H**), 4.55 (1H, dd, *J* = 2.5, 1.5 Hz, Ar**H**), 4.37 (1H, t, *J* = 2.5 Hz, Ar**H**), 4.15 (5H, s, Ar**H**), 3.63 (3H, s, OC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 164.4 (C), 136.5 (2 x C), 132.1 (C), 131.2 (2 x CH), 130.3 (2 x CH), 128.0 (2 x CH), 128.0 (CH), 127.5 (2 x CH), 126.8 (CH), 117.9 (C), 88.0 (C), 72.6 (C), 71.8 (CH), 69.9 (5 x CH), 66.3 (CH), 66.2 (CH), 63.1 (CH_3); HRMS (ES) Exact mass calcd for $C_{26}H_{22}FeNO_2$ $[M+H]^+$: 436.0995, found: 436.0992.

Ferrocenecarboxamide 3.89[330]



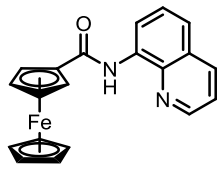
R_f 0.29 (pet. ether/EtOAc 1:4); m.p. 165 °C (lit. 168-170 °C)[330]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.72 (2H, s, N**H**$_2$), 4.69 (2H, s, Ar**H**), 4.39 (2H, s, Ar**H**), 4.24 (5H, s, Ar**H**); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 172.9 (C), 74.5 (C), 70.9 (2 x CH), 69.9 (5 x CH), 68.6 (2 x CH). Data consistent with literature.[330]

3,4-Diphenyl-1*H*,2*H*-ferrocenyl[1,2-*a*]pyridin-1-one 3.92



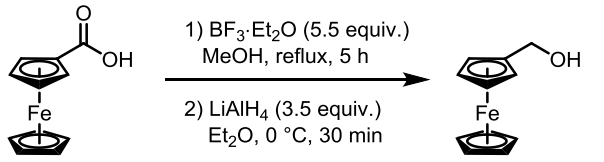
R_f 0.33 (pet. ether/EtOAc 1:1); IR (film, cm^{-1}) 3184, 3057, 2928, 2249, 1653 (C=O), 1599, 1497, 1443, 1308, 1238; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (1H, s, N**H**), 7.35-7.23 (8H, m, Ar**H**), 7.23-7.17 (2H, m, Ar**H**), 5.24 (1H, dd, *J* = 2.5, 1.0 Hz, Ar**H**), 4.64 (1H, dd, *J* = 2.5, 1.0 Hz, Ar**H**), 4.40 (1H, t, *J* = 2.5 Hz, Ar**H**), 4.14 (5H, s, Ar**H**); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 169.2 (C), 136.6 (C), 135.5 (C), 133.3 (C), 130.4 (2 x CH), 129.0 (2 x CH), 128.6 (2 x CH), 128.4 (3 x CH), 127.0 (CH), 116.7 (C), 90.4 (C), 72.0 (CH), 71.0 (C), 70.0 (5 x CH), 66.5 (CH), 65.6 (CH); HRMS (ES) Exact mass calcd for $C_{25}H_{20}FeNO$ $[M+H]^+$: 406.0889, found: 406.0886.

***N*-(Quinolin-8-yl)ferrocenecarboxamide 3.94**



General procedure D was applied to ferrocencecarboxylic acid **3.75** (200 mg, 0.869 mmol), 8-aminoquinoline (114 mg, 0.790 mmol), EDC·HCl (167 mg, 0.869 mmol) and DMAP (cat., 1 crystal). The residue was purified by flash chromatography (toluene/EtOAc 99:1→95:5) to give *quinoline amide* **3.94** as an orange solid (166 mg, 59%). R_f 0.23 (pet. ether/EtOAc 9:1); m.p. 121-123 °C; IR (film, cm^{-1}) 3352, 3090, 2245, 1667 (C=O), 1526, 1485, 1423, 1383, 1327, 1271; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.31 (1H, br s, N**H**), 8.90 (1H, d, *J* = 3.0 Hz, Ar**H**), 8.82 (1H, d, *J* = 7.0 Hz, Ar**H**), 8.20 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.59 (1H, t, *J* = 7.5 Hz, Ar**H**), 7.56-7.48 (2H, m, Ar**H**), 4.98 (2H, s, Ar**H**), 4.48 (2H, s, Ar**H**), 4.30 (5H, s, Ar**H**); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 148.3 (CH), 138.6 (C), 136.4 (CH), 134.7 (C), 128.0 (C), 127.6 (CH), 121.6 (CH), 121.0 (CH), 116.2 (CH), 70.9 (2 x CH), 70.0 (5 x CH), 68.6 (2 x CH); HRMS (ES) Exact mass calcd for $C_{20}H_{17}FeN_2O$ $[M+H]^+$: 357.0685, found: 357.0682.

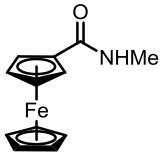
1-(Hydroxymethyl)-ferrocene 3.95[331]



3.75 **3.95**
65% over 2 steps

To ferrocenecarboxylic acid **3.75** (200 mg, 0.87 mmol) in methanol (6.0 mL) was added boron trifluoride etherate (0.60 mL) and the reaction was heated at reflux for 5 h. Sat. aq. $NaHCO_3$ (6 mL) was added until the pH of the solution was 8-9 and the aqueous phase extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were washed with brine (30 mL), dried (Na_2SO_4) and the solvent removed *in vacuo* to give methyl ester which was used in the next step without further purification. To methyl ester (200 mg, 0.82 mmol) in anhydrous diethyl ether (5 mL) at 0 °C under nitrogen was added lithium aluminium hydride (2.2 M in 2-MeTHF, 1.3 mL, 2.9 mmol) dropwise. The reaction was stirred for 30 min and quenched carefully with potassium sodium tartrate (20 mL) and allowed to stir for 15 min. The phases were separated and the aqueous phase extracted with EtOAc (3 x 50 mL). The combined organics were dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified using flash chromatography (pet. ether/EtOAc 4:1→3:1) to give alcohol **3.95** (117 mg, 65% over 2 steps) as a yellow solid. R_f 0.21 (pet. ether/Et_2O); m.p. 70 °C (lit. 78-80 °C)[332]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.34 (2H, d, *J* = 5.0 Hz, Ar**H**), 4.25 (2H, t, *J* = 2.0 Hz, Ar**H**), 4.20-4.17 (7H, m, Ar**H**, C**H**$_2$OH); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 88.3 (C), 68.2 (2 x CH), 68.2 (5 x CH), 67.9 (2 x CH), 60.7 (CH_2). Data consistent with literature.[331]

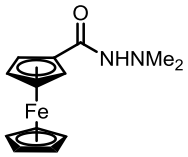
***N*-Methylferrocenecarboxamide 3.96**[333]



General procedure B (method 2) was applied to methylamine hydrochloride (293 mg, 4.34 mmol), triethylamine (1.81 mL, 13.0 mmol) and ferrocenecarboxylic acid chloride **3.76** (500 mg, 2.17 mmol) in CH_2Cl_2 (2.5 mL). The reaction was stirred for 4 h and the residue was purified by flash

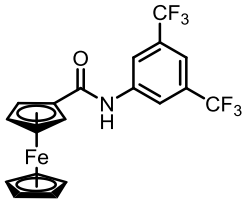
chromatography (pet. ether/EtOAc 3:1→1:2) to give amide **3.96** (360 mg, 68%) as a brown solid. R_f 0.16 (pet. ether/EtOAc 1:1); m.p. 175 °C (decomp.) (lit. 185-187 °C)[333]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.74 (1H, br s, N**H**), 4.67 (2H, s, Ar**H**), 4.34 (2H, s, Ar**H**), 4.21 (5H, s, Ar**H**), 2.96 (3H, s, C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ (CO and COC resonances not resolved) 70.3 (2 x CH), 69.7 (5 x CH), 68.0 (2 x CH), 26.4 (CH_3). Data consistent with literature.[333]

***N',N'*-Dimethylferrocenecarbohydrazide 3.97**



General procedure B was applied to *N*,*N*-dimethylhydrazine (70 µL, 0.97 mmol), *N*-methylmorpholine (0.11 mL, 0.97 mmol) and ferrocenecarboxylic acid chloride **3.76** (200 mg, 0.81 mmol) in CH_2Cl_2 (5 mL). The reaction was stirred at room temperature for 7 h and the residue was purified by flash chromatography (pet. ether/acetone/NEt_3 70:30:1→10:90:1) to give *hydrazide* **AJ-3-78** (163 mg, 74%) as an orange solid. R_f 0.34 (pet. ether/acetone 7:3); m.p. 165 °C (decomp.); IR (film, cm^{-1}) 1636 (C=O), 1539, 1466, 1445, 1377, 1292, 1221, 1167, 1105, 1049; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.44 (1H, br s, N**H**), 4.68 (2H, s, Ar**H**), 4.35 (2H, s, Ar**H**), 4.21 (5H, s, Ar**H**), 2.69 (6H, s, N(C**H**$_3$)$_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 168.2 (C), 74.7 (C), 70.4 (2 x CH), 69.7 (5 x CH), 68.1 (2 x CH), 47.7 (2 x CH_3); HRMS (ES) Exact mass calcd for $C_{13}H_{17}FeN_2O$ $[M+H]^+$: 273.0685, found: 273.0687.

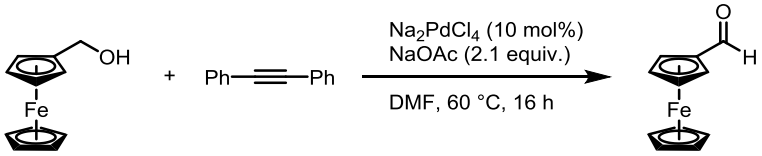
***N*-[3,5-Bis(trifluoromethyl)phenyl]ferrocenecarboxamide 3.98**



General procedure B was applied to 3,5-bis(trifluoromethyl)aniline (0.13 mL, 0.81 mmol), triethylamine (0.11 mL, 0.81 mmol) and ferrocenecarboxylic acid chloride **3.76** (240 mg, 0.966 mmol) in CH_2Cl_2 (10 mL). The reaction was stirred for 24 h and the residue purified by recrystallisation (hexane/EtOAc) to give *aryl amide* **3.98** (108 mg, 30%) as an orange solid. R_f 0.31 (pet. ether/EtOAc 9:1); m.p. 235 °C (decomp.); IR (film, cm^{-1})

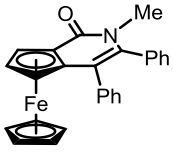
1645 (C=O), 1638, 1533, 1476, 1460, 1408, 1377, 1298, 1275, 1188; ^{1}H NMR (500 MHz, CD_3OD) δ 8.40 (2H, s, Ar**H**), 7.66 (1H, s, Ar**H**), 5.03 (2H, t, *J* = 1.5 Hz, Ar**H**), 4.86 (5H, s, Ar**H**), 4.54 (2H, t, *J* = 2.0 Hz, Ar**H**); ^{13}C NMR (125.8 MHz, CD_3OD) δ (CO and COC resonances not resolved) 172.8 (C), 142.3 (C), 133.2 (q, $^{1}J_{C\text{-}F}$ = 34.0 Hz, 2 x C), 125.9 (C), 123.7 (C), 121.0 (CH), 121.0 (CH), 117.4 (CH), 75.9 (C), 72.7 (2 x CH), 71.0 (5 x CH), 69.9 (2 x CH); ^{19}F NMR (376 MHz, $(CD_3)_2CO$) δ −64.1; HRMS (ES) Exact mass calcd for $C_{19}H_{14}F_6FeNO$ $[M+H]^+$: 442.0324, found: 442.0324.

Ferrocenecarboxaldehyde 3.100[332]



General procedure C was applied to 1-(hydroxymethyl)-ferrocene **3.95** (11 mg, 50 μmol), sodium tetrachloropalladate (1.5 mg, 10 mol%), sodium acetate (9 mg, 0.11 mmol) and diphenylacetylene (10 mg, 55 μmol). The residue was purified by flash chromatography (pet. ether/Et_2O 4:1→2:1) to give aldehyde **3.100** (4 mg, 37%) as an orange solid. R_f 0.34 (pet. ether/EtOAc 9:1); m.p. 108 °C (lit. 129-131 °C)[332]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.97 (1H, s, C**H**O), 4.81 (2H, t, *J* = 2.0 Hz, Ar**H**), 4.62 (2H, t, *J* = 2.0 Hz, Ar**H**), 4.29 (5H, s, Ar**H**); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ (2 x CH resonances not resolved) 193.4 (C), 79.4 (C), 73.2 (2 x CH), 69.6 (5 x CH). Data consistent with literature.[332]

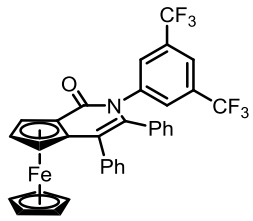
2-Methyl-3,4-diphenyl-1*H*-2*H*-ferrocenyl[1,2-*a*]pyridin-1-one 3.101



General procedure C was applied to ferrocenecarboxamide **3.96** (73 mg, 0.30 mmol), sodium tetrachloropalladate (9 mg, 10 mol%), sodium acetate (52 mg, 0.63 mmol) and diphenylacetylene (59 mg, 0.33 mmol). The residue was purified by flash chromatography (pet. ether/EtOAc 4:1→1:4) to give *pyridinone* **3.101** (6 mg, 5%) as an orange solid. R_f 0.62 (pet. ether/EtOAc 1:1); m.p. 98 °C

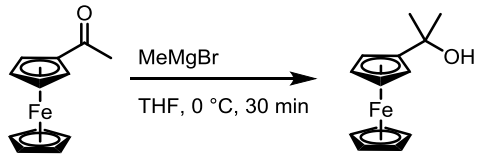
(decomp.); IR (film, cm^{-1}) 3059, 2922, 2853, 2243, 1651 (C=O), 1589, 1493, 1443, 1414, 1315; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.13 (9H, m, Ar**H**), 7.10-7.05 (1H, m, Ar**H**), 5.27 (1H, dd, *J* = 2.5, 1.0 Hz, Ar**H**), 4.49 (1H, dd, *J* = 2.5, 1.5 Hz, Ar**H**), 4.32 (1H, t, *J* = 2.5 Hz, Ar**H**), 4.11 (5H, s, Ar**H**), 3.24 (3H, s, NC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 169.1 (C), 137.9 (C), 137.3 (C), 135.5 (C), 130.6 (CH), 130.4 (CH), 130.2 (2 x CH), 128.2 (CH), 128.0 (CH), 128.0 (CH), 127.8 (2 x CH), 126.4 (CH), 118.5 (C), 89.0 (C), 72.0 (C), 71.3 (CH), 69.7 (5 x CH), 65.8 (CH), 65.7 (CH), 33.7 (CH_3); HRMS (ES) Exact mass calcd for $C_{26}H_{22}FeNO$ $[M+H]^+$: 420.1045, found: 420.1044.

2-[3,5-Bis(trifluoromethyl)phenyl]-3,4-diphenyl-1*H*,2*H*-ferrocenyl[1,2-*a*]pyridin-1-one 3.102



General procedure C was applied to ferrocenecarboxamide **3.98** (132 mg, 0.30 mmol), sodium tetrachloropalladate (9 mg, 10 mol%), sodium acetate (52 mg, 0.63 mmol) and diphenylacetylene (59 mg, 0.33 mmol). The residue was purified by flash chromatography (toluene) to give *pyridinone* **3.102** (23 mg, 12%) as an orange solid. R_f 0.31 (9:1 toluene/CH_2Cl_2); m.p. 120 °C (decomp.); IR (film, cm^{-1}) 3059, 2926, 1672 (C=O), 1589, 1493, 1466, 1445, 1373, 1308, 1277; ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 7.89 (2H, s, Ar**H**), 7.79 (1H, s, Ar**H**), 7.40-6.93 (10H, s, Ar**H**), 5.19 (1H, dd, *J* = 2.5, 1.5 Hz, Ar**H**), 4.55 (1H, dd, *J* = 2.5, 1.5 Hz, Ar**H**), 4.53 (1H, t, *J* = 2.5 Hz, Ar**H**), 4.31 (5H, s, Ar**H**); ^{13}C NMR (125.8 MHz, $(CD_3)_2CO$) δ 168.8 (C), 143.3 (C), 138.1 (C), 137.8 (C), 136.1 (C), 132.9 (CH), 132.5 (3 x CH), 131.9 (q, $^{1}J_{C\text{-}F}$ = 34.0 Hz, 2 x C), 131.4 (2 x CH), 129.0 (2 x CH), 128.4 (2 x CH), 128.4 (CH), 127.7 (CH), 125.3 (C), 121.4 (quin, $^{3}J_{C\text{-}F}$ = 4.0 Hz, CH), 120.0 (C), 90.0 (C), 72.8 (CH), 72.2 (C), 71.1 (5 x CH), 67.6 (CH), 67.2 (CH); ^{19}F NMR (376 MHz, $(CD_3)_2CO$) δ −63.6 to −64.3 (m, 2 x CF_3); HRMS (ES) Exact mass calcd for $C_{33}H_{22}F_6FeNO$ $[M+H]^+$: 618.0950, found: 618.0966.

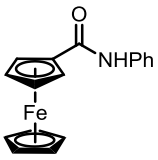
2-Ferrocenylpropan-2-ol 3.104[334]



3.103 **3.104** 55%

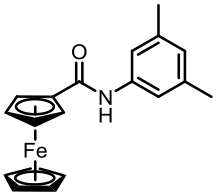
To a stirred solution of acetylferrocene **3.103** (200 mg, 0.88 mmol) in anhydrous THF (10 mL) at 0 °C under nitrogen was added methylmagnesium bromide (3.0 M in Et_2O, 0.58 mL, 1.8 mmol) dropwise. The reaction was stirred for 30 min and quenched with sat. aq. NH_4Cl (10 mL). The phases were separated and the aqueous phase extracted with EtOAc (3 x 10 mL). The combined organics were dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by flash chromatography (toluene/EtOAc 99:1→97:3) to give alcohol **3.104** (118 mg, 55%) as a yellow solid. R_f 0.85 (pet. ether/EtOAc 1:1); m.p. 56-58 °C (lit. 56-58 °C)[334]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.21 (5H, s, Ar**H**), 4.20 (2H, t, *J* = 2.0 Hz, Ar**H**), 4.17 (2H, t, *J* = 2.0 Hz, Ar**H**), 1.51 (6H, s, C(C**H**$_3$)$_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 100.1 (C), 68.8 (C), 68.2 (5 x CH), 67.7 (2 x CH), 65.5 (2 x CH), 30.8 (2 x CH_3). Data consistent with literature.[334]

***N*-Phenylferrocenecarboxamide 3.106**[335]



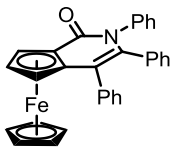
General procedure D was applied to ferrocenecarboxylic acid **3.75** (200 mg, 0.869 mmol), aniline (72 µL, 0.79 mmol), EDC·HCl (167 mg, 0.869 mmol) and DMAP (cat., 1 crystal). The residue was purified by recrystallisation (hexane/EtOAc) to give *N*-phenyl amide **3.106** (123 mg, 53%) as a yellow powder. R_f 0.16 (pet. ether/EtOAc 9:1); m.p. 199 °C (decomp.) (lit. 211 °C)[335]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (2H, d, *J* = 7.5 Hz, Ar**H**), 7.42 (1H, br s, N**H**), 7.37 (2H, t, *J* = 7.0 Hz, Ar**H**), 7.14 (1H, t, *J* = 6.5 Hz, Ar**H**), 4.80 (2H, s, Ar**H**), 4.43 (2H, s, Ar**H**), 4.27 (5H, s, Ar**H**); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 168.6 (C), 138.1 (C), 129.0 (2 x CH) 124.0 (CH), 119.7 (2 x CH), 76.2 (C), 70.9 (2 x CH), 69.9 (5 x CH), 68.3 (2 x CH). Data consistent with literature.[335]

_N_-(3,5-Dimethylphenyl)ferrocenecarboxamide 3.107



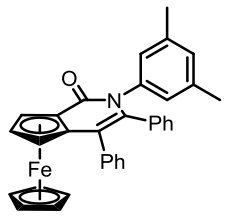
General procedure D was applied to ferrocencecarboxylic acid **3.75** (200 mg, 0.869 mmol), 3,5-dimethylaniline (98 µL, 0.79 mmol), EDC·HCl (167 mg, 0.869 mmol) and DMAP (cat., 1 crystal). The residue was purified by recrystallisation (hexane/EtOAc) to give *arylamide* **3.107** (139 mg, 53%) as a yellow solid. R_f 0.23 (pet. ether/EtOAc 9:1); m.p. 215 °C (decomp.); IR (film, cm^{-1}) 3285, 1638 (C=O), 1614, 1547, 1533, 1462, 1422, 1377, 1317, 1290; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83-7.70 (4H, m, Ar**H**, N**H**), 5.29 (2H, s, Ar**H**), 4.94 (2H, s, Ar**H**), 4.78 (5H, s, Ar**H**), 2.82 (6H, s, 2 x C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 168.4 (C), 138.8 (2 x C), 137.9 (C), 125.7 (CH), 117.4 (2 x CH), 76.6 (C), 71.1 (2 x CH), 70.1 (5 x CH), 68.5 (2 x CH), 21.4 (2 x CH_3); HRMS (ES) Exact mass calcd for $C_{19}H_{20}FeNO$ $[M+H]^+$: 334.0889, found: 334.0891.

2,3,4-Triphenyl-1*H*,2*H*-ferrocenyl[1,2-*a*]pyridin-1-one 3.108



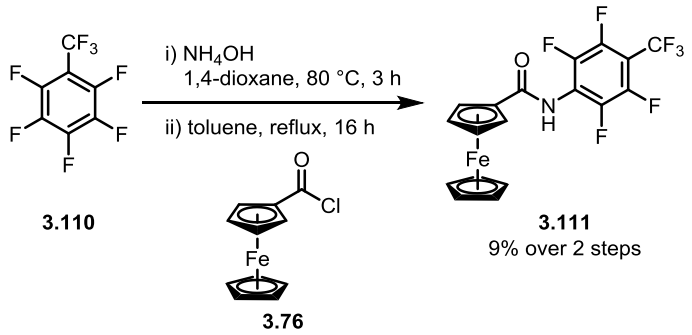
General procedure C was applied to ferrocenecarboxamide **3.106** (92 mg, 0.30 mmol), sodium tetrachloropalladate (9 mg, 10 mol%), sodium acetate (52 mg, 0.63 mmol) and diphenylacetylene (59 mg, 0.33 mmol). The residue was purified by flash chromatography (pet. ether/EtOAc 9:1→3:1 and then CH_2Cl_2) to give *pyridinone* **3.108** (19 mg, 13%) as an orange solid. R_f 0.24 (pet. ether/EtOAc 4:1); m.p. 150 °C (decomp.); IR (film, cm^{-1}) 3059, 2920, 2241, 1663 (C=O), 1585, 1491, 1443, 1314, 1287, 1213; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26-7.01 (10H, m, Ar**H**), 6.97-6.82 (2H, m, Ar**H**), 5.30 (1H, dd, *J* = 2.5, 1.0 Hz, Ar**H**), 4.59 (1H, dd, *J* = 2.5, 1.0 Hz, Ar**H**), 4.40 (1H, t, *J* = 2.5 Hz, Ar**H**), 4.22 (5H, s, Ar**H**); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 168.7 (C), 139.7 (C), 137.9 (C), 137.3 (C), 135.2 (C), 131.4 (2 x CH), 130.3 (2 x CH), 130.0 (2 x CH), 128.3 (2 x CH), 127.9 (2 x CH), 127.1 (3 x CH), 127.0 (CH), 126.5 (CH), 118.5 (C), 89.1 (C), 71.7 (C), 71.7 (CH), 70.0 (5 x CH), 66.4 (CH), 66.4 (CH); HRMS (ES) Exact mass calcd for $C_{31}H_{24}FeNO$ $[M+H]^+$: 482.1202, found: 482.1205.

2-(3,5-Dimethylphenyl)-3,4-diphenyl-1*H*,2*H*-ferrocenyl[1,2-*a*]pyridin-1-one 3.109



General procedure C was applied to ferrocenecarboxamide **3.107** (100 mg, 0.30 mmol), sodium tetrachloropalladate (9 mg, 10 mol%), sodium acetate (52 mg, 0.63 mmol) and diphenylacetylene (59 mg, 0.33 mmol). The residue was purified by flash chromatography (toluene/EtOAc 19:1→9:1 and then CH_2Cl_2) to give *pyridinone* **3.109** (18 mg, 12%) as an orange solid. R_f 0.39 (CH_2Cl_2); m.p. 175 °C (decomp.); IR (film, cm^{-1}) 3057, 3028, 2918, 2241, 1663 (C=O), 1612, 1585, 1493, 1443, 1325; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26-7.11 (5H, m, Ar**H**), 6.99-6.82 (5H, m, Ar**H**), 6.78-6.61 (3H, m, Ar**H**), 5.30-5.27 (1H, m, Ar**H**), 4.60-4.55 (1H, m, Ar**H**), 4.41-4.36 (1H, m, Ar**H**), 4.22 (5H, s, Ar**H**), 2.22 (3H, s, C**H**$_3$), 2.13 (3H, s, C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 168.7 (C), 139.2 (C), 138.1 (C), 137.8 (C), 137.7 (C), 137.4 (C), 135.3 (C), 131.4 (2 x CH), 130.3 (2 x CH), 128.8 (CH), 127.8 (2 x CH), 127.6 (2 x CH), 126.9 (3 x CH), 126.4 (CH), 118.3 (C), 89.1 (C), 71.9 (C), 71.5 (CH), 70.0 (5 x CH), 66.3 (CH), 66.2 (CH), 21.1 (CH_3), 21.0 (CH_3); HRMS (ES) Exact mass calcd for $C_{33}H_{27}FeNONa$ $[M+Na]^+$: 532.1334, found: 532.1333.

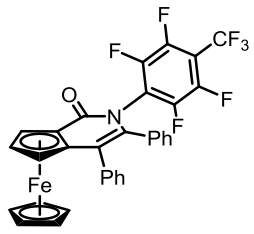
***N*-[2,3,5,6-Tetrafluoro-4-(trifluoromethyl)phenyl]ferrocenecarboxamide 3.111**



To a stirred solution of octafluorotoluene **3.110** (0.50 mL, 3.5 mmol) in 1,4-dioxane (5 mL) was added aq. NH_4OH (35%, 0.88 mL, 6.4 mmol). The reaction was heated to 80 °C and stirred for 3 h. The reaction was cooled and the solvent removed *in vacuo*. The residue was diluted with H_2O (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organics were

dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash chromatography (pet. ether → pet. ether/EtOAc 4:1) to give aniline (283 mg, 34%) as a colourless oil. To a stirred solution of aniline (283 mg, 1.21 mmol) in anhydrous toluene (5 mL) under nitrogen was added ferrocenecarboxylic acid chloride **3.76** (274 mg, 1.10 mmol). The reaction was heated at reflux for 16 h, diluted with CH_2Cl_2 (20 mL) and washed with 1 N HCl (20 mL). The organic phase was dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by flash chromatography (pet. ether/EtOAc 95:5→80:20) to give *arylamide* **3.111** (128 mg, 26%) as an orange solid. R_f 0.30 (pet. ether/EtOAc 4:1); m.p. 159-161 °C; IR (film, cm^{-1}) 3264, 1668 (C=O), 1651, 1510, 1477, 1443, 1425, 1340, 1288, 1236; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (1H, br s, N**H**), 4.86 (2H, s, Ar**H**), 4.54 (2H, s, Ar**H**), 4.31 (5H, s, Ar**H**); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 168.4 (d, J = 7.5 Hz, $^4C_{C\text{-}F}$, C), 144.5 (dd, $^1J_{C\text{-}F}$ = 260.0 Hz, $^2J_{C\text{-}F}$ = 13.5 Hz, 2 x C), 141.8 (dd, $^1J_{C\text{-}F}$ = 253.5 Hz, $^2J_{C\text{-}F}$ = 12.0 Hz, 2 x C), 120.9 (q, $^1J_{C\text{-}F}$ = 282.0 Hz, C), 120.8 (t, $^2J_{C\text{-}F}$ = 14.0 Hz, C), 107.2-106.1 (m, C), 72.9 (C), 72.0 (2 x CH), 70.3 (5 x CH), 69.0 (2 x CH); ^{19}F NMR (376 MHz, $CDCl_3$) δ −56.1 (t, $^4J_{F\text{-}F}$ = 21.5 Hz, CF_3), −140.7 to −140.1 (m, 2 x CF), −143.7 to −144.1 (m, 2 x CF); HRMS (ES) Exact mass calcd for $C_{18}H_{11}F_7FeNO$ $[M+H]^+$: 446.0073, found: 446.0073.

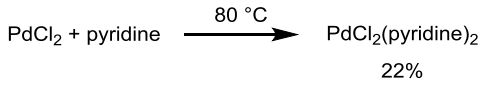
2-[2,3,5,6-Tetrafluoro-4-(trifluoromethyl)phenyl]-3,4-diphenyl-1*H*-2*H*-ferrocenyl[1,2-*a*]pyridin-1-one 3.112



General procedure C was applied to ferrocenecarboxamide **3.111** (80 mg, 0.18 mmol), sodium tetrachloropalladate (5 mg, 10 mol%), sodium acetate (31 mg, 0.38 mmol) and diphenylacetylene (35 mg, 0.20 mmol). The residue was purified by flash chromatography (pet. ether/Et_2O 99:1→1:1) to give *pyridinone* **3.112** (4 mg, 4%) as an orange solid. R_f 0.44 (pet. ether/Et_2O 4:1); m.p. 160 °C (decomp.); IR (film, cm^{-1}) 2918, 2849, 1686 (C=O), 1593, 1504, 1445, 1425, 1342, 1302, 1275; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27-6.98 (10H, m,

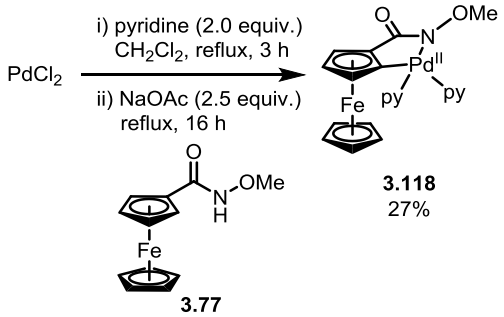
Ar**H**), 5.32 (1H, dd, *J* = 2.5, 1.0 Hz, Ar**H**), 4.62 (1H, dd, *J* = 2.5, 1.0 Hz, Ar**H**), 4.50 (1H, t, *J* = 2.5 Hz, Ar**H**), 4.25 (5H, s, Ar**H**); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ (3 x CF resonances not resolved) 167.4 (C), 143.9 (dd, $^{1}J_{C\text{-}F}$ = 250.0 Hz, $^{2}J_{C\text{-}F}$ = 13.5 Hz, C), 130.0 (CH), 129.9 (CH), 129.7 (CH), 128.8 (CH), 128.1 (2 x CH), 128.1 (CH), 127.9 (CH), 127.1 (CH), 125.5 (CH), 123.8 (t, $^{2}J_{C\text{-}F}$ = 15.0 Hz, C), 120.3 (C), 88.6 (C), 72.5 (CH), 70.5 (5 x CH), 70.0 (C), 67.5 (CH), 66.9 (CH); ^{19}F NMR (376 MHz, $CDCl_3$) δ −56.5 (t, $^{4}J_{F\text{-}F}$ = 22.0 Hz, CF_3), −140.2 (ddd, $^{3}J_{C\text{-}F}$ = 23.0 Hz, *J* = 11.0 Hz, *J* = 3.0 Hz, F), −141.0 (dddd, *J* = 22.0 Hz, *J* = 22.0 Hz, *J* = 11.0 Hz, *J* = 7.0 Hz, F), −141.4 (dddd, *J* = 22.5 Hz, *J* = 22.0 Hz, *J* = 11.0 Hz, *J* = 7.0 Hz, F), −142.2 (ddd, $^{3}J_{C\text{-}F}$ = 23.0 Hz, *J* = 11.0 Hz, *J* = 3.0 Hz, F); HRMS (EI) Exact mass calcd for $C_{32}H_{19}F_7FeNO$ $[M+H]^+$: 621.0621, found: 621.0610.

$PdCl_2$(pyridine)$_2$[336]



Palladium chloride (100 mg, 0.564 mmol) was suspended in pyridine (4 mL) under nitrogen and the reaction stirred at 80 °C for 30 min. The mixture was filtered and hexane (10 mL) added to the filtrate. The filtrate was left for 16 h and the precipitate collected, washed with hexane, and dried to give $PdCl_2$(pyridine)$_2$ (42 mg, 22%) as a yellow powder. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.87-8.84 (4H, m, Ar**H**), 7.82-7.78 (2H, m, Ar**H**), 7.38-7.34 (4H, m, Ar**H**); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 153.4 (4 x CH), 138.6 (2 x CH), 125.0 (4 x CH). Data consistent with literature.[336]

Palladacycle 3.118

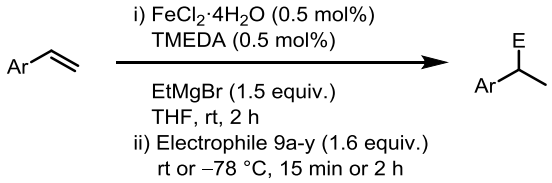


To a solution of palladium chloride (100 mg, 0.564 mmol) in CH_2Cl_2 (10 mL) under nitrogen was added pyridine (90 µL, 1.1 mmol) and the reaction heated at reflux for 3 h. Sodium acetate (116 mg, 1.41 mmol) and ferrocenylamide **3.77** (248 mg, 0.959 mmol) were added and the reaction heated at reflux for 16 h. The solvent was removed *in vacuo* and the residue purified by flash chromatography (silica doped with 1% pyridine, CH_2Cl_2→*i*-PrOH/EtOAc 2:8→water/ *i*-PrOH /EtOAc 1:2:7) to give *palladacyle* **3.118** (56 mg, 27%) as a yellow solid. R_f 0.30 (water/ *i*-PrOH /EtOAc 1:2:7); m.p. 165 °C (decomp.); IR (film, cm^{-1}) 1599 (C=O), 1483, 1445, 1416, 1354, 1344, 1294, 1279, 1219, 1153; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.91 (2H, d, *J* = 5.0 Hz, Ar**H**), 8.62 (2H, d, *J* = 5.0 Hz, Ar**H**), 7.91 (1H, t, *J* = 7.5 Hz, Ar**H**), 7.81 (1H, t, *J* = 7.5 Hz, Ar**H**), 7.47 (2H, t, *J* = 7.0 Hz, Ar**H**), 7.36 (2H, t, *J* = 6.5 Hz), 4.67 (1H, br s, C**H**), 4.29 (5H, s, Ar**H**), 3.97 (1H, apt t, *J* = 2.0 Hz, Ar**H**), 3.48 (1H, s, Ar**H**), 3.19 (3H, s, OC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 177.6 (C), 152.7 (2 x CH), 150.9 (2 x CH), 138.3 (CH), 138.1 (CH), 125.6 (2 x CH), 124.9 (2 x CH), 87.5 (C), 80.8 (C), 69.6 (5 x CH), 69.1 (CH), 66.1 (CH), 65.9 (CH), 61.0 (CH_3); HRMS (ES) Exact mass calcd for $C_{22}H_{22}FeN_3O_2Pd$ $[M+H]^+$: 522.0091, found: 522.0105.

6.4 Hydromagnesiation for the Hydrofunctionalisation of Alkenes

6.4.1 General Procedures

General Procedure A: Second generation hydrofunctionalisation of styrenes



Method 1

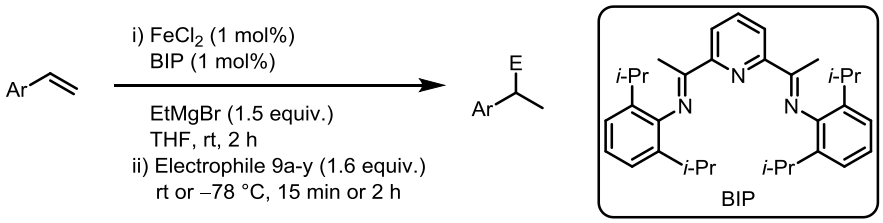
To a stirred solution of $FeCl_2 \cdot 4H_2O$ (7 mg, 0.04 mmol) in anhydrous THF (5 mL) under nitrogen was added *N*,*N*,*N*',*N*'-tetramethylethylenediamine (TMEDA) (5 µL, 0.04 mmol) and stirred for 5 mins. 0.5 mL of this solution was transferred to a flask containing 4.5 mL anhydrous THF under nitrogen. A styrene derivative (0.7 mmol) was added to the flask and ethylmagnesium bromide (3 M in THF, 0.35 mL, 1.1 mmol) was added dropwise. The reaction was stirred for 2 h and the electrophile (1.1 mmol) added, either neat or as a solution in anhydrous THF (1 M), at room temperature or at −78 °C. The reaction was stirred for a further 15 min (with Me_3SiCl) or 2 h (with any other electrophile) and quenched with aqueous sulphate buffer solution or water (5 mL). The phases were separated and the aqueous phase extracted with Et_2O (3 x 5 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash chromatography.

Method 2

To a stirred solution of $FeCl_2 \cdot 4H_2O$ (10 mg, 0.05 mmol) in anhydrous THF (5 mL) under nitrogen was added *N*,*N*,*N*',*N*'-tetramethylethylenediamine (TMEDA) (7 µL, 0.05 mmol) and stirred for 5 mins. 0.5 mL of this solution was transferred to a flask containing 6.5 mL anhydrous THF under nitrogen. 3-Methoxystyrene (0.14 mL, 1.0 mmol) was added to the flask and ethylmagnesium bromide (3 M in THF, 0.50 mL, 1.5 mmol) was added dropwise. The reaction was stirred for 2 h and the electrophile (1.6 mmol) added, either neat or as a solution in anhydrous THF (1 M), at room temperature or at −78 °C. The reaction was stirred

for a further 15 min (with Me_3SiCl) or 2 h (with other electrophiles) and quenched with aqueous sulphate buffer solution or water (10 mL). The phases were separated and the aqueous phase extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash chromatography.

General Procedure B: First generation hydrofunctionalisation of styrenes



To a stirred solution of $FeCl_2$ (1 mg, 0.007 mmol) in anhydrous THF (5 mL) under nitrogen was added bis(imino)pyridine (BIP) (3 mg, 0.007 mmol) and stirred for 5 mins. A styrene derivative (0.7 mmol) was added to the flask and ethylmagnesium bromide (3 M in THF, 0.35 mL, 1.1 mmol) was added dropwise. The reaction was stirred for 2 h and the electrophile (1.1 mmol) added, either neat or as a solution in anhydrous THF (1 M), at room temperature or at −78 °C. The reaction was stirred for a further 15 min (with Me_3SiCl) or 2 h (with any other electrophile) and quenched with aqueous sulphate buffer solution or water (5 mL). The phases were separated and the aqueous phase extracted with Et_2O (3 x 5 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash chromatography.

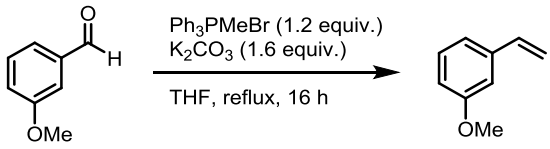
6.4.2 Data

Trimethyl(1-phenylethyl)silane 4.68[337]

General procedure A (method 1) was applied to styrene **4.67** (80 µL, 0.7 mmol), $FeCl_2 \cdot 4H_2O$ (0.7 mg, 0.004 mmol), TMEDA (0.5 µL, 0.004 mmol),

ethylmagnesium bromide (3 M in THF, 0.35 mL, 1.1 mmol) and trimethylsilyl chloride (0.14 mL, 1.1 mmol) to give silane **4.68** (91% yield by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27-7.22 (2H, m, Ar**H**), 7.12-7.07 (1H, m, Ar**H**), 7.07-7.03 (2H, m, Ar**H**), 2.17 (1H, q, *J* = 7.5 Hz, C**H**CH_3), 1.37 (3H, d, *J* = 7.5 Hz, CHC**H**$_3$), −0.05(9H, s, Si(C**H**$_3$)$_3$). Data consistent with literature.[337]

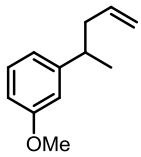
1-Ethenyl-3-methoxybenzene 4.71[226]



4.70 **4.71** 95%

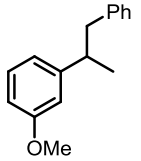
To a stirred suspension of potassium carbonate (8.12 g, 58.8 mmol) and methyltriphenylphosphonium bromide (15.7 g, 44.0 mmol) in anhydrous THF (50 mL) under nitrogen was added *m*-anisaldehyde **4.70** (4.48 mL, 36.7 mmol). The reaction was heated at reflux for 16 h, cooled, filtered and the solvent removed *in vacuo*. The residue was dissolved in hot pentane (50 mL), cooled to 0 °C to precipitate triphenylphosphine oxide, filtered and washed with cold pentane (20 mL). The filtrate was concentrated *in vacuo* and passed through a short plug of silica gel (pet. ether/Et_2O 9:1) to give 3-methoxystyrene **4.71** (4.69 g, 95%) as a colourless oil. R_f 0.76 (pet. ether/EtOAc 9:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29-7.24 (1H, m, Ar**H**), 7.06-7.01 (1H, m, Ar**H**), 7.00-6.96 (1H, m, Ar**H**), 6.87-6.82 (1H m, Ar**H**), 6.72 (1H, dd, *J* = 17.5, 11.0 Hz, C**H**=CH_2), 5.77 (1H, d, *J* = 17.5 Hz, CH=C**H**$_a$H$_b$), 5.28 (1H, d, *J* = 11.0 Hz, CH=CH$_a$**H**$_b$), 3.85 (3H, s, OC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 159.8 (C), 139.0 (C), 136.8 (CH), 129.5 (CH), 118.9 (CH), 114.1 (CH_2), 113.4 (C), 111.5 (CH), 55.2 (CH_3). Data consistent with literature.[226]

1-Methoxy-3-(pent-4-en-2-yl)benzene 4.74



General procedure A (method 2) was applied to 3-methoxystyrene **4.71** (0.14 mL, 1.0 mmol), $FeCl_2 \cdot 4H_2O$ (1 mg, 0.005 mmol), TMEDA (0.7 µL, 0.005 mmol), ethylmagnesium bromide (3 M in THF, 0.50 mL, 1.5 mmol) and allyl bromide **4.73** (0.14 mL, 1.6 mmol). The crude product was purified by flash chromatography (pentane→pentane/Et_2O 99.8:0.2) to give **4.74** as a colourless oil (143 mg, 81%). R_f 0.55 (pentane/Et_2O 99:1); IR (film, cm^{-1}) 3075, 2959, 2926, 2835, 1639, 1601, 1584, 1487, 1452, 1437; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (1H, t, *J* = 8.0 Hz, Ar**H**), 6.81 (1H, d, *J* = 7.5 Hz, Ar**H**), 6.79-6.73 (2H, m, Ar**H**), 5.79-5.68 (1H, m, C**H**=CH_2), 5.05-4.95 (2H, m, CH=C**H**$_2$), 3.82 (3H, s, OC**H**$_3$), 2.78 (1H, sex., *J* = 7.0 Hz, C**H**CH_3), 2.44-2.38 (1H, m, C**H**$_a$H$_b$CHCH_3), 2.33-2.25 (1H, m, CH$_a$**H**$_b$CHCH_3), 1.26 (3H, d, *J* = 7.0 Hz, C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 159.8 (C), 148.8 (C), 137.1 (CH), 129.2 (CH), 119.4 (CH), 115.9 (CH_2), 113.0 (CH), 110.9 (CH), 55.1 (CH_3), 42.6 (CH_2), 39.8 (CH), 21.4 (CH_3); HRMS (ES) Exact mass calcd for $C_{12}H_{17}O$ $[M+H]^+$: 177.1274, found: 177.1266.

1-Methoxy-3-(1-phenylpropan-2-yl)benzene 4.76

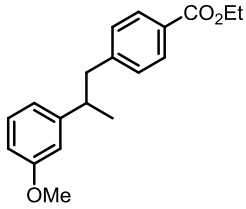


General procedure A (method 2) was applied to 3-methoxystyrene **4.71** (0.14 mL, 1.0 mmol), $FeCl_2 \cdot 4H_2O$ (1 mg, 0.005 mmol), TMEDA (0.7 µL, 0.005 mmol), ethylmagnesium bromide (3 M in THF, 0.50 mL, 1.5 mmol) and benzyl bromide **4.75** (0.19 mL, 1.6 mmol) was added at −78 °C. The crude product was purified by flash chromatography (pentane→pentane/Et_2O 99.5:0.5) to give **4.76** as a colourless oil (193 mg, 85%). R_f 0.38 (pentane/Et_2O 99:1); IR (film, cm^{-1}) 3026, 2959, 2928, 2833, 1601, 1584, 1487, 1452, 1435, 1260; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.16 (4H, m, Ar**H**), 7.14-7.10 (2H, m, Ar**H**), 6.82 (1H, d, *J* = 7.5 Hz, Ar**H**), 6.78-6.74 (2H, m, Ar**H**), 3.80 (3H, s, OC**H**$_3$), 3.00 (1H, sex., *J* = 7.0 Hz, C**H**CH_3), 2.97 (1H, dd, *J* = 13.0, 6.5 Hz, C**H**$_a$H$_b$Ph), 2.78 (1H, dd, *J* = 12.5, 8.0 Hz, CH$_a$**H**$_b$Ph), 1.26 (3H, d, *J* = 7.0 Hz, CHC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 159.5 (C), 148.7 (C), 140.8 (C), 129.2 (CH),

129.1 (2 x CH), 128.1 (2 x CH), 125.8 (CH), 119.5 (CH), 113.0 (CH), 111.1 (CH), 55.1 (CH_3), 45.0 (CH_2), 41.9 (CH), 21.1 (CH_3); HRMS (ES) Exact mass calcd for $C_{16}H_{18}ONa$ $[M+Na]^+$: 249.1250, found: 249.1250.

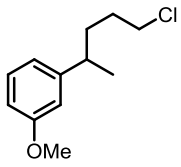
General procedure A (method 2) was applied to 3-methoxystyrene **4.71** (0.14 mL, 1.0 mmol), $FeCl_2{\cdot}4H_2O$ (1.0 mg, 0.5 mol%), TMEDA (0.7 µL, 0.5 mol%), ethylmagnesium bromide (3 M in THF, 0.50 mL, 1.5 mmol) and benzyl chloride **4.77** (0.18 mL, 1.6 mmol) was added at −78 °C. The crude product was purified by flash chromatography (pentane→pentane/Et_2O 99.5:0.5) to give **4.76** as a colourless oil (207 mg, 91%).

Ethyl 4-[2-(3-methoxyphenyl)propyl]benzoate 4.79



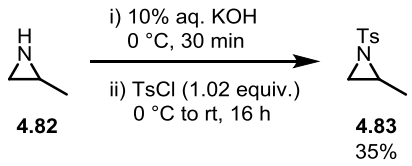
General procedure A (method 2) was applied to 3-methoxystyrene **4.71** (0.14 mL, 1.0 mmol), $FeCl_2{\cdot}4H_2O$ (1 mg, 0.005 mmol), TMEDA (0.7 µL, 0.005 mmol), ethylmagnesium bromide (3 M in THF, 0.50 mL, 1.5 mmol) and ethyl 4-(bromomethyl)benzoate **4.78** (389 mg, 1.6 mmol) in THF (2 mL) was added at −78 °C. The crude product was purified by flash chromatography (pet. ether/Et_2O 99:1→80:20) to give **4.79** as a colourless oil (155 mg, 54%). R_f 0.46 (pet. ether/Et_2O 9:1); IR (film, cm^{-1}) 2961, 2932, 1715 (C=O), 1609, 1585, 1485, 1456, 1368, 1275, 1179; ^1H NMR (500 MHz, $CDCl_3$) δ 7.92 (2H, d, *J* = 8.5 Hz, Ar**H**), 7.20 (1H, t, *J* = 8.0 Hz, Ar**H**), 7.14 (2H, d, *J* = 8.5 Hz, Ar**H**), 6.78-6.70 (3H, m, Ar**H**), 4.36 (2H, q, *J* = 7.0 Hz, OC**H**$_2$CH$_3$), 3.79 (3H, s, OC**H**$_3$), 3.01 (1H, sex., *J* = 7.0 Hz, C**H**CH$_3$), 2.98 (1H, dd, *J* = 13.0, 7.0 Hz, C**H**$_a$H$_b$Ar), 2.84 (1H, dd, *J* = 12.5, 7.0 Hz, CH$_a$**H**$_b$Ar), 1.39 (3H, t, *J* = 7.0 Hz, OCH$_2$C**H**$_3$), 1.25 (3H, d, *J* = 7.0 Hz, CHC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 166.7 (C), 159.6 (C), 148.0 (C), 146.1 (C), 129.4 (2 x CH), 129.3 (CH), 129.1 (2 x CH), 128.2 (C), 119.4 (CH), 113.0 (CH), 111.1 (CH), 60.8 (CH_2), 55.1 (CH_3), 44.9 (CH_2), 41.7 (CH), 21.2 (CH_3), 14.3 (CH_3); HRMS (ES) Exact mass calcd for $C_{19}H_{22}O_3Na$ $[M+Na]^+$: 321.1461, found: 321.1471.

1-(5-Chloropentan-2-yl)-3-methoxybenzene 4.81



General procedure A (method 2) was applied to 3-methoxystyrene **4.71** (0.14 mL, 1.0 mmol), $FeCl_2 \cdot 4H_2O$ (1 mg, 0.005 mmol), TMEDA (0.7 µL, 0.005 mmol), ethylmagnesium bromide (3 M in THF, 0.50 mL, 1.5 mmol) and 1-chloro-3-iodopropane **4.80** (0.17 mL, 1.6 mmol). The crude product was purified by flash chromatography (pentane→pentane/Et_2O 99:1) to give **4.81** as a colourless oil (132 mg, 62%). R_f 0.55 (pet. ether/Et_2O 19:1); IR (film, cm^{-1}) 2957, 2934, 2835, 1601, 1584, 1485, 1452, 1435, 1256, 1043; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (1H, t, *J* = 8.0 Hz, Ar**H**), 6.79 (1H, d, *J* = 7.5 Hz, Ar**H**), 6.77-6.74 (2H, m, Ar**H**), 3.82 (3H, s, OC**H**$_3$), 3.53-3.46 (2H, m, C**H**$_2$Cl), 2.70 (1H, q, *J* = 7.0 Hz, C**H**CH_3), 1.80-1.62 (4H, m C**H**$_2$C**H**$_2$Cl), 1.27 (3H, d, *J* = 7.0 Hz, CHC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 159.7 (C), 148.6 (C), 129.4 (CH), 119.4 (CH), 113.0 (CH), 111.0 (CH), 55.1 (CH_3), 45.2 (CH_2), 39.5 (CH), 35.3 (CH_2), 30.8 (CH_2), 22.4 (CH_3); HRMS (EI) Exact mass calcd for $C_{12}H_{17}ClO$ $[M]^+$: 212.0962, found: 212.0967.

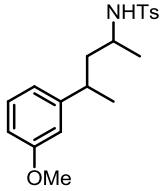
2-Methyl-1-(4-methylbenzenesulfonyl)aziridine 4.83[338]



To a 10% aq. KOH solution (20 mL) at 0 °C was added 2-methylaziridine **4.82** (2.48 mL, 35.0 mmol) and the reaction stirred for 30 min. Tosyl chloride (6.81 g, 35.7 mmol) was added and the reaction stirred for 30 min at 0 °C, and for 16 h at room temperature. The white precipitate was filtered, washed multiple times with water and dried under high vacuum. The product was purified by recrystallisation (pet. ether) to give tosyl aziridine **4.83** as a colourless solid (2.58 g, 35%). R_f 0.38 (pet. ether/Et_2O 3:1); m.p. 58 °C (pet. ether) (lit. 60-61 °C)[338]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (2H, d, *J* = 8.5, 2.0 Hz, Ar**H**), 7.34 (2H, d, *J* = 8.0 Hz, Ar**H**), 2.86-2.79 (1H, m, C**H**CH_3), 2.61 (1H, dd, *J* = 7.0, 2.5 Hz,

C**H**$_a$H$_b$CH), 2.44 (3H, s, $SO_2C_6H_4C\mathbf{H}_3$), 2.02 (1H, dd, *J* = 4.5, 1.5 Hz, CH$_a$**H**$_b$CH), 1.25 (3H, dd, *J* = 5.5, 2.5 Hz, CHC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 144.3 (C), 135.4 (C), 129.6 (2 x CH), 127.8 (2 x CH), 35.8 (CH), 34.7 (CH_2), 21.6 (CH_3), 16.7 (CH_3). Data consistent with literature.[338]

***N*-[4-(3-methoxyphenyl)pentan-2-yl]-4-methylbenzene-1-sulfonamide 4.84**



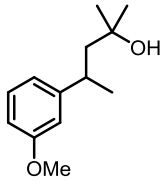
General procedure A (method 2) was applied to 3-methoxystyrene **4.71** (0.14 mL, 1.0 mmol), $FeCl_2 \cdot 4H_2O$ (1 mg, 0.005 mmol), TMEDA (0.7 µL, 0.005 mmol), ethylmagnesium bromide (3 M in THF, 0.50 mL, 1.5 mmol) and tosyl aziridine **4.83** (338 mg, 1.6 mmol). The crude product (1:1 dr) was purified by flash chromatography (pet. ether/Et_2O 9:1→1:2) to give **4.84** as a colourless oil and 1:1 mixture of diastereomers (271 mg, 78%). R_f 0.17 (pet. ether/Et_2O 2:1); IR (film, cm^{-1}) 3279 (NH), 2963, 1597, 1485, 1454, 1431, 1319, 1288, 1258, 1157; HRMS (EI) Exact mass calcd for $C_{19}H_{25}NO_3S$ $[M]^+$: 347.1550, found: 347.1542.

Diastereomer A: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72-7.63 (2H, m, Ar**H**), 7.31-7.24 (2H, m, Ar**H**), 7.21-7.13 (1H, m, Ar**H**), 6.77-6.71 (1H, m, Ar**H**), 6.67-6.59 (2H, m, Ar**H**), 4.24 (1H, m, N**H**), 3.81 (3H, s, OC**H**$_3$), 3.29-3.14 (1H, m, C**H**NHTs), 2.82-2.73 (1H, m, ArC**H**CH$_3$), 2.44 (3H, s, $SO_2C_6H_4C\mathbf{H}_3$), 1.68-1.55 (2H, m, C**H**$_2$CHCH$_3$), 1.16 (3H, d, *J* = 7.0 Hz, ArCHC**H**$_3$), 0.97 (3H, d, *J* = 6.5 Hz, CHNHTsC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 159.7 (C), 148.0 (C), 143.2 (C), 138.3 (C), 129.6 (2 x CH), 129.4 (CH), 127.1 (2 x CH), 119.3 (CH), 113.1 (CH), 111.3 (CH), 55.1 (CH_3), 48.6 (CH), 46.4 (CH_2), 36.4 (CH), 22.7 (CH_3), 22.3 (CH_3), 21.5 (CH_3).

Diastereomer B: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72-7.63 (2H, m, Ar**H**), 7.31-7.24 (2H, m, Ar**H**), 7.21-7.13 (1H, m, Ar**H**), 6.77-6.71 (1H, m, Ar**H**), 6.67-6.59 (2H, m, Ar**H**), 4.24 (1H, m, N**H**), 3.81 (3H, s, OC**H**$_3$), 3.29-3.14 (1H, m, C**H**NHTs), 2.67 (1H, sex., *J* = 7.0 Hz, ArC**H**CH$_3$), 2.43 (3H, s, $SO_2C_6H_4C\mathbf{H}_3$), 1.77 (1H, ddd, *J* = 14.0, 8.0, 7.0 Hz, C**H**$_a$H$_b$CHCH$_3$), 1.67-1.56 (1H, m, CH$_a$**H**$_b$CHCH$_3$), 1.13 (3H, d, *J* = 7.0 Hz, ArCHC**H**$_3$), 1.03

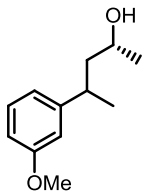
(3H, d, *J* = 7.0 Hz, CHNHTsC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 159.8 (C), 147.9 (C), 143.2 (C), 137.9 (C), 129.6 (2 x CH), 129.5 (CH), 127.1 (2 x CH), 119.2 (CH), 112.7 (CH), 111.3 (CH), 55.1 (CH_3), 48.2 (CH), 46.9 (CH_2), 36.6 (CH), 22.5 (CH_3), 21.8 (CH_3), 21.5 (CH_3).

4-(3-Methoxyphenyl)-2-methylpentan-2-ol 4.85



General procedure A (method 2) was applied to 3-methoxystyrene **4.71** (0.14 mL, 1.0 mmol), $FeCl_2 \cdot 4H_2O$ (1 mg, 0.005 mmol), TMEDA (0.7 µL, 0.005 mmol), ethylmagnesium bromide (3 M in THF, 0.50 mL, 1.5 mmol) and 2,2-dimethyloxirane **4.85** (0.14 mL, 1.6 mmol). The crude product was purified by flash chromatography ($CH_2Cl_2 \rightarrow CH_2Cl_2$/MeOH 99:1) to give **4.86** as a colourless oil (146 mg, 70%). R_f 0.52 (pet. ether/Et_2O 1:1); IR (film, cm^{-1}) 3418 (O-H), 2963, 2928, 2835, 1599, 1584, 1485, 1454, 1437, 1375; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (1H, t, *J* = 8.0 Hz, Ar**H**), 6.87-6.83 (1H, m, Ar**H**), 6.81-6.79 (1H, m, Ar**H**), 6.74 (1H, ddd, *J* = 8.0, 2.5, 1.0 Hz, Ar**H**), 3.81 (3H, s, OC**H**$_3$), 2.95 (1H, dqd, *J* = 9.0, 7.0, 4.5 Hz, C**H**CH_3), 1.98 (1H, dd, *J* = 14.5, 9.0 Hz, C**H**$_a$H$_b$C$(CH_3)_2$OH), 1.77 (1H, dd, *J* = 14.5, 4.5 Hz, CH$_a$**H**$_b$C$(CH_3)_2$OH), 1.28 (3H, d, *J* = 7.0 Hz, CHC**H**$_3$), 1.18 (3H, s, $CH_2C(C\mathbf{H}_3)_a(CH_3)_b$OH), 1.15 (3H, s, $CH_2C(CH_3)_a(C\mathbf{H}_3)_b$OH); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 159.8 (C), 149.8 (C), 129.6 (CH), 119.5 (CH), 113.1 (CH), 111.0 (CH), 71.4 (C), 55.1 (CH_3), 51.2 (CH_2), 36.5 (CH), 29.9 (2 x CH_3), 25.0 (CH_3); HRMS (ES) Exact mass calcd for $C_{13}H_{20}O_2Na$ $[M+Na]^+$: 231.1356, found: 231.1367.

(2*R*)-4-(3-Methoxyphenyl)pentan-2-ol 4.88



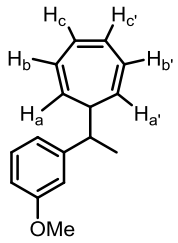
General procedure A (method 2) was applied to 3-methoxystyrene **4.71** (0.14 mL, 1.0 mmol), $FeCl_2 \cdot 4H_2O$ (1 mg, 0.005 mmol), TMEDA (0.7 µL, 0.005 mmol), ethylmagnesium bromide (3 M in THF, 0.50 mL, 1.5 mmol) and (*R*)-(+)-propylene oxide **4.87** (0.11 mL, 1.6 mmol). The crude product (1:1 dr) was purified by flash chromatography (pet. ether/Et_2O 3:1→1:1) to give **4.88** as a colourless oil and 1:1

mixture of diastereomers (139 mg, 71%). R_f 0.29 (pet. ether/Et_2O 3:1); IR (film, cm^{-1}) 3368 (O-H), 2961, 2926, 2835, 1599, 1584, 1485, 1454, 1437, 1375; HRMS (ES) Exact mass calcd for $C_{12}H_{18}O_2Na$ $[M+Na]^+$: 217.1199, found: 217.1182.

Diastereomer A ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (1H, t, *J* = 8.0 Hz, Ar**H**), 6.82 (1H, d, *J* = 7.5 Hz, Ar**H**), 6.79-6.73 (2H, m, Ar**H**), 3.81 (3H, s, OC**H**$_3$), 3.62-3.55 (1H, m, C**H**OH), 3.00-2.92 (1H, m, C**H**CH_3), 1.72-1.68 (2H, m, C**H**$_2$$CHCH_3$), 1.34 (1H, br. s, O**H**), 1.27 (3H, d, *J* = 7.0 Hz, ArCHC**H**$_3$), 1.14 (3H, d, *J* = 6.0 Hz, CHC**H**$_3$OH); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 159.7 (C), 148.6 (C), 129.4 (CH), 119.5 (CH), 113.1 (CH), 110.9 (CH), 65.9 (CH), 55.1 (CH_3), 47.5 (CH_2), 36.6 (CH), 24.1 (CH_3), 23.0 (CH_3).

Diastereomer B ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (1H, t, *J* = 8.0 Hz, Ar**H**), 6.82 (1H, d, *J* = 7.5 Hz, Ar**H**), 6.79-6.73 (2H, m, Ar**H**), 3.81 (3H, s, OC**H**$_3$), 3.83-3.75 (1H, m, C**H**OH), 2.85 (1H, sex., *J* = 7.0 Hz, ArC**H**CH_3), 1.83 (1H, td, *J* = 14.0, 7.5 Hz, C**H**$_a$$H_b$$CHCH_3$), 1.65 (1H, ddd, *J* = 14.0, 7.5, 5.0 Hz, C**H**$_a$$H_b$$CHCH_3$), 1.34 (1H, br. s, O**H**), 1.27 (3H, d, *J* = 7.0 Hz, CHC**H**$_3$OH), 1.20 (3H, d, *J* = 6.0 Hz, CHC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 159.8 (C), 149.0 (C), 129.5 (CH), 119.2 (CH), 112.9 (CH), 111.1 (CH), 66.4 (CH), 55.1 (CH_3), 47.8 (CH_2), 37.0 (CH), 23.7 (CH_3), 22.2 (CH_3).

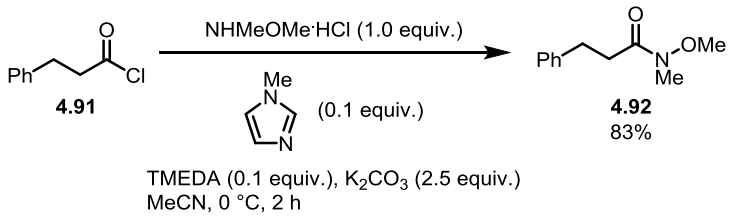
7-[1-(3-Methoxyphenyl)ethyl]cyclohepta-1,3,5-triene 4.90



General procedure A (method 2) was applied to 3-methoxystyrene **4.71** (0.14 mL, 1.0 mmol), $FeCl_2 \cdot 4H_2O$ (1 mg, 0.005 mmol), TMEDA (0.7 µL, 0.005 mmol), ethylmagnesium bromide (3 M in THF, 0.50 mL, 1.5 mmol) and the benzylic Grignard intermediate was added to tropylium tetrafluoroborate **4.89** (285 mg, 1.6 mmol) in THF (2 mL). The crude product was purified by flash chromatography (pentane → pentane/Et_2O 98:2) to give **4.90** as a colourless oil (190 mg, 84%). R_f 0.25 (pentane/Et_2O 99:1); IR (film, cm^{-1}) 3013, 2961, 2833, 1601, 1584, 1485, 1452, 1435, 1287, 1261; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (1H, t, *J* = 8.0 Hz, Ar**H**), 6.81-6.76 (2H, m, Ar**H**), 6.75-6.73 (1H, m, Ar**H**), 6.71 (1H, dd, *J* = 11.0, 5.5 Hz, C**H**$_a$), 6.67

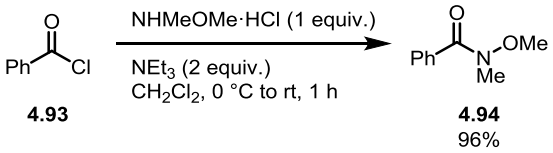
(1H, dd, *J* = 11.0, 5.5 Hz, C**H**$_{a'}$), 6.28 (1H, dd, *J* = 9.5, 5.5 Hz, C**H**$_b$), 6.07 (1H, dd, *J* = 9.5, 5.5 Hz, C**H**$_{b'}$), 5.37 (1H, dd, *J* = 9.5, 5.5 Hz, C**H**$_c$), 5.08 (1H, dd, *J* = 9.5, 6.0 Hz, C**H**$_{c'}$), 3.81 (3H, s, OC**H**$_3$), 3.00 (1H, qd, *J* = 10.5, 7.0 Hz, C**H**CH$_3$), 1.76 (1H, td, *J* = 11.0, 5.5 Hz, C**H**CHCH$_3$), 1.38 (3H, d, *J* = 7.0 Hz, CHC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 159.7 (C), 147.8 (C), 131.0 (CH), 130.6 (CH), 129.4 (CH), 125.5 (CH), 124.9 (CH), 124.9 (CH), 124.2 (CH), 120.1 (CH), 113.8 (CH), 111.1 (CH), 55.1 (CH_3), 45.3 (CH), 42.3 (CH), 20.9 (CH_3); HRMS (EI) Exact mass calcd for $C_{16}H_{18}O$ $[M]^+$: 226.1352, found: 226.1357.

_N_-Methoxy-_N_-methyl-3-phenyl-propionamide 4.92[339]



To a suspension of amine (500 mg, 5.13 mmol), 1-methylimdazole (41 µL, 0.51 mmol), TMEDA (76 µL, 0.51 mmol) and K_2CO_3 (1.78 g, 12.8 mmol) in anhydrous acetonitrile (5 mL) at 0 °C was added hydrocinnamoyl chloride **4.91** (1.14 mL, 7.70 mmol). The mixture was stirred at 0 °C for 2 h and water (10 mL) added. The phases were separated and the aqueous phase extracted with EtOAc (3 x 10 mL). The combined organics were washed with water (40 mL) and brine (40 mL) and the solvent removed *in vacuo*. The product was purified by flash chromatography (pet. ether/EtOAc 4:1→1:1) to give Weinreb amide **4.92** (823 mg, 83%) as a colourless oil. R_f 0.27 (pet. ether/EtOAc 3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.28 (2H, m, Ar**H**), 7.26-7.23 (2H, m, Ar**H**), 7.23-7.19 (1H, m, Ar**H**), 3.61 (3H, s, OC**H**$_3$), 3.19 (3H, s, NC**H**$_3$), 2.98 (2H, t, *J* = 7.5 Hz, PhC**H**$_2$), 2.76 (2H, t, *J* = 7.5 Hz, C**H**$_2$CO); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 173.7 (C), 141.3 (C), 128.4 (4 x CH), 126.0 (CH), 61.2 (CH_3), 33.8 (CH_2), 32.2 (CH_3), 30.7 (CH_2). Data consistent with literature.[339]

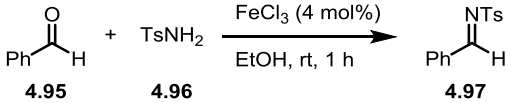
_N_-Methoxy-_N_-methyl-benzamide 4.94[274]



4.93 **4.94** 96%

To a stirred suspension of NHMeOMe·HCl (980 mg, 10 mmol) in anhydrous CH_2Cl_2 (25 mL) at 0 °C was added triethylamine (2.8 mL, 20 mmol) and benzoyl chloride **4.93** (1.2 mL, 10 mmol) dropwise. The reaction was stirred at 0 °C for 15 min and warmed to room temperature over 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ (25 mL) and the phases separated. The organic phase was washed with 1 M HCl (25 mL) and brine (25 mL). The organic phase was dried (Na_2SO_4) and the solvent removed *in vacuo* to give crude amide. The product was purified by flash chromatography (pet. ether/EtOAc 19:1→2:1) to give Weinreb amide **4.94** (1.59 g, 96%) as a colourless oil. R_f 0.35 (pet. ether/EtOAc 9:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70-7.64 (2H, m, Ar**H**), 7.48-7.43 (1H, m, Ar**H**), 7.43-7.37 (2H, m, Ar**H**), 3.56 (3H, s, OC**H**$_3$), 3.36 (3H, s, NC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 169.9 (C), 134.1 (C), 130.5 (CH), 128.1 (2 x CH), 128.0 (2 x CH), 61.0 (CH_3), 33.8 (CH_3). Data consistent with literature.[274]

4-Methyl-N-(phenylmethylidene)benzene-1-sulfonamide 4.97[275]

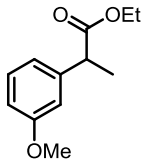


4.95 **4.96** **4.97** 55%

To a solution of amine **4.96** (1.00 g, 5.84 mmol) in ethanol (20 mL) was added $FeCl_3$ (38 mg, 4 mol%) and benzaldehyde **4.95** (1.19 mL, 11.7 mmol). The reaction was stirred for 1 h and the solvent removed *in vacuo*. The residue was dissolved in EtOAc (20 mL) and washed with sat. aq. $NaHCO_3$ (3 x 20 mL). The organic phase was dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude reaction mixture was purified by flash chromatography (pet. ether/EtOAc 9:1→1:1) to give imine **4.97** (837 mg, 55%) as a colourless solid. R_f 0.57 (pet. ether/EtOAc 3:1); m.p. 104-106 °C (lit. 107 °C)[340]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.04

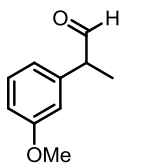
(1H, s, C**H**N), 7.94 (2H, dd, *J* = 8.5, 1.5 Hz, Ar**H**), 7.90 (2H, d, *J* = 8.5 Hz, Ar**H**), 7.62 (1H, tt, *J* = 7.5, 1.5 Hz, Ar**H**), 7.50 (2H, t, *J* = 8.0 Hz, Ar**H**), 7.36 (2H, d, *J* = 8.0 Hz, Ar**H**), 2.45 (3H, s, C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 170.1 (CH), 144.6 (C), 135.2 (C), 134.9 (CH), 132.4 (C), 131.3 (2 x CH), 129.8 (2 x CH), 129.1 (2 x CH), 128.1 (2 x CH), 21.6 (CH_3). Data consistent with literature.[275]

2-(3-Methoxyphenyl)propanoic acid ethyl ester 4.102[341]



General procedure A (method 2) was applied to 3-methoxystyrene **4.71** (0.14 mL, 1.0 mmol), $FeCl_2 \cdot 4H_2O$ (1 mg, 0.005 mmol), TMEDA (0.7 µL, 0.005 mmol), ethylmagnesium bromide (3 M in THF, 0.50 mL, 1.5 mmol) and ethyl chloroformate (0.15 mL, 1.6 mmol). The crude product was purified by flash chromatography (pet. ether/Et_2O 99:1→94:6) to give **4.102** as a colourless oil (157 mg, 75%). R_f 0.26 (pet. ether/Et_2O 9:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (1H, t, *J* = 8.0 Hz, Ar**H**), 6.92-6.89 (1H, m, Ar**H**), 6.87 (1H, t, *J* = 2.0 Hz, Ar**H**), 6.81 (1H, ddd, *J* = 8.0, 2.5, 1.0 Hz, Ar**H**), 4.16 (1H, dq, *J* = 11.0, 7.0 Hz, OC**H**$_a$H$_b$CH$_3$), 4.11 (1H, dq, *J* = 11.0, 7.0 Hz, OCH$_a$**H**$_b$CH$_3$), 3.81 (3H, s, OC**H**$_3$), 3.69 (1H, q, *J* = 7.0 Hz, C**H**CH$_3$), 1.50 (3H, d, *J* = 7.0 Hz, CHC**H**$_3$), 1.22 (3H, t, *J* = 7.0 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 174.4 (C), 159.7 (C), 142.2 (C), 129.5 (CH), 119.8 (CH), 113.2 (CH), 112.4 (CH), 60.7 (CH_2), 55.2 (CH_3), 45.6 (CH), 18.6 (CH_3), 14.1 (CH_3). Data consistent with literature.[341]

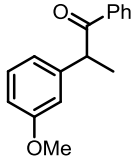
2-(3-Methoxyphenyl)-propionaldehyde 4.104[342]



General procedure A (method 2) was applied to 3-methoxystyrene **4.71** (0.14 mL, 1.0 mmol), $FeCl_2 \cdot 4H_2O$ (1 mg, 0.005 mmol), TMEDA (0.7 µL, 0.005 mmol), ethylmagnesium bromide (3 M in THF, 0.50 mL, 1.5 mmol) and *N*,*N*-dimethylformamide (0.12 mL, 1.6 mmol). The crude product was purified by flash chromatography (pet. ether/Et_2O 99:1→90:10) to give **4.104** as a colourless oil (105 mg,

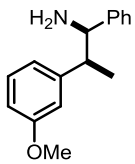
64%). R_f 0.31 (pet. ether/Et2O 9:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.68 (1H, d, *J* = 1.5 Hz, C**H**O), 7.31 (1H, t, *J* = 8.0 Hz, Ar**H**), 6.86 (1H, ddd, *J* = 8.5, 2.5, 1.0 Hz, Ar**H**), 6.82 (1H, d, *J* = 8.0 Hz, Ar**H**), 6.76 (1H, t, *J* = 2.0 Hz, Ar**H**), 3.82 (3H, s, OC**H**$_3$), 3.61 (1H, dq, *J* = 7.0, 1.0 Hz, C**H**CH_3), 1.45 (3H, d, *J* = 7.0 Hz, CHC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 200.8 (CH), 160.1 (C), 139.2 (C), 130.0 (CH), 120.6 (CH), 114.1 (CH), 112.7 (CH), 55.2 (CH_3), 53.0 (CH), 14.5 (CH_3). Data consistent with literature.[342]

2-(3-Methoxyphenyl)-1-phenylpropan-1-one 4.106[343]



General procedure A (method 2) was applied to 3-methoxystyrene **4.71** (0.14 mL, 1.0 mmol), $FeCl_2 \cdot 4H_2O$ (1 mg, 0.005 mmol), TMEDA (0.7 µL, 0.005 mmol), ethylmagnesium bromide (3 M in THF, 0.50 mL, 1.5 mmol) and benzonitrile (0.16 mL, 1.6 mmol). The crude product was purified by flash chromatography (pet. ether/Et_2O 99:1→95:5) to give **4.106** as a colourless oil (156 mg, 65%); R_f 0.32 (pet. ether/Et_2O 19:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (2H, dd, *J* = 8.0, 1.0 Hz, Ar**H**), 7.51-7.46 (1H, m, Ar**H**), 7.41-7.37 (2H, m, Ar**H**), 7.22 (1H, t *J* = 8.0 Hz, Ar**H**), 6.89 (1H, d, *J* = 8.0 Hz, Ar**H**), 6.83 (1H, t, *J* = 2.0 Hz, Ar**H**), 6.75 (1H, ddd, *J* = 8.0, 2.5, 1.0 Hz, Ar**H**), 4.66 (1H, q, *J* = 7.0 Hz, C**H**CH_3), 3.78 (3H, s, OC**H**$_3$), 1.54 (3H, d, *J* = 7.0 Hz, CHC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 200.1 (C), 160.0 (C), 143.0 (C), 136.5 (C), 132.7 (CH), 129.9 (CH), 128.7 (2 x CH), 128.5 (2 x CH), 120.2 (CH), 113.5 (CH), 112.1 (CH), 55.2 (CH_3), 47.9 (CH), 19.4 (CH_3). Data consistent with literature.[343]

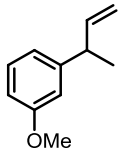
2-(3-Methoxyphenyl)-1-phenylpropan-1-amine 4.108



General procedure A (method 2) was applied to 3-methoxystyrene **4.71** (0.14 mL, 1.0 mmol), $FeCl_2 \cdot 4H_2O$ (1 mg, 0.005 mmol), TMEDA (0.7 µL, 0.005 mmol), ethylmagnesium bromide (3 M in THF, 0.50 mL, 1.5 mmol) and benzonitrile (0.16 mL, 1.6 mmol). The reaction was quenched with anhydrous MeOH (2 mL) and sodium borohydride added (64 mg, 1.7 mmol). The reaction was stirred for 2 h and

quenched with water (10 mL). The phases were separated and the aqueous phase extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude product was purified by flash chromatography (pet. ether/EtOAc 1:1→EtOAc) to give **4.108** as a colourless oil (132 mg, 55%) and as a single diastereomer; R_f 0.48 (EtOAc); IR (film, cm^{-1}) 2961, 2833, 1599, 1584, 1487, 1452, 1437, 1281, 1261, 1155; ^{1}H NMR (500 MHz, CD_3OD) δ 7.41-7.38 (2H, m, Ar**H**), 7.38-7.33 (2H, m, Ar**H**), 7.30-7.25 (2H, m, Ar**H**), 6.92 (1H, d, *J* = 7.5 Hz, Ar**H**), 6.89-6.86 (1H, m, Ar**H**), 6.82 (1H, dd, *J* = 8.0, 2.5 Hz, Ar**H**), 3.93 (1H, d, *J* = 9.5 Hz, C**H**NH_2), 3.80 (3H, s, OC**H**$_3$), 2.91 (1H, dq, *J* = 9.5, 7.0 Hz, C**H**CH_3), 0.98 (3H, d, *J* = 7.0 Hz, CHC**H**$_3$); ^{13}C NMR (125.8 MHz, CD_3OD) δ 161.5 (C), 147.5 (C), 144.9 (C), 130.7 (CH), 129.5 (2 x CH), 128.7 (2 x CH), 128.5 (CH), 120.0 (CH), 114.7 (CH), 113.1 (CH), 63.4 (CH), 55.6 (CH_3), 49.1 (CH), 19.9 (CH_3); HRMS (ES) Exact mass calcd for $C_{16}H_{19}NONa$ $[M+Na]^+$: 264.1359, found: 264.1366. The relative stereochemistry was determined by comparing this ^{1}H NMR data with previously reported data.[276]

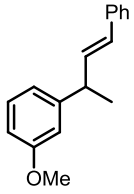
1-(But-3-en-2-yl)-3-methoxybenzene 4.115[344]



General procedure A (method 2) was applied to 3-methoxystyrene **4.71** (0.14 mL, 1.0 mmol), $FeCl_2 \cdot 4H_2O$ (1 mg, 0.005 mmol), TMEDA (0.7 µL, 0.005 mmol), ethylmagnesium bromide (3 M in THF, 0.50 mL, 1.5 mmol) and vinyl bromide (1 M in THF, 1.6 mL, 1.6 mmol). The crude product was purified by flash chromatography (pentane→pentane/Et_2O 98:2) to give alkene **4.115** as a colourless oil (124 mg, 76%). R_f 0.63 (pet. ether/Et_2O 99:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (1H, t, *J* = 8.0 Hz, Ar**H**), 6.83 (1H, d, *J* = 7.5Hz, Ar**H**), 6.80-6.74 (2H, m, Ar**H**), 6.01 (1H, ddd, *J* = 17.0, 10.5, 6.5 Hz, C**H**=CH_2), 5.10-5.03 (2H, m, CH=C**H**$_2$), 3.81 (3H, s, OC**H**$_3$), 3.46 (1H, app. quintet, *J* = 7.0 Hz, C**H**CH_3), 1.37 (3H, d, *J* = 7.0 Hz, CHC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 159.7 (C), 147.3 (C), 143.1 (CH), 129.3 (CH), 119.7 (CH), 113.2 (CH), 113.2 (CH_2), 111.2 (CH), 55.1 (CH_3), 43.2 (CH), 20.7 (CH_3). Data consistent with

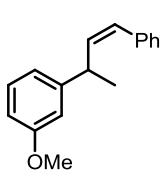
literature.[344]

1-Methoxy-3-[(3*E*)-4-phenylbut-3-en-2-yl]benzene 4.117[345]

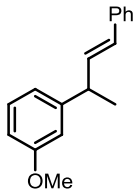


General procedure A (method 2) was applied to 3-methoxystyrene **4.71** (0.14 mL, 1.0 mmol), $FeCl_2 \cdot 4H_2O$ (1 mg, 0.005 mmol), TMEDA (0.7 µL, 0.005 mmol), ethylmagnesium bromide (3 M in THF, 0.50 mL, 1.5 mmol) and *β*-bromostyrene (0.21 mL, 1.6 mmol). The crude product was purified by flash chromatography (pentane→pentane/Et_2O 99:1) to give alkene **4.117** as a yellow oil (187 mg, 78%). R_f 0.48 (pet. ether/Et_2O 99:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.35 (2H, m, Ar**H**), 7.30 (2H, t, *J* = 7.5 Hz, Ar**H**), 7.26-7.19 (2H, m, Ar**H**), 6.89 (1H, d, *J* = 7.5 Hz, Ar**H**), 6.86-6.83 (1H, m, Ar**H**), 6.77 (1H, dd, *J* = 8.0, 2.5 Hz, Ar**H**), 6.44 (1H, d, *J* = 16.0 Hz, C**H**Ph), 6.38 (1H, dd, *J* = 16.0, 6.0 Hz, C**H**=CHPh), 3.82 (3H, s, OC**H**$_3$), 3.63 (1H, quintet, *J* = 7.0 Hz, C**H**CH_3), 1.47 (3H, d, *J* = 7.0 Hz, CHC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 159.7 (C), 147.4 (C), 137.6 (C), 135.0 (CH), 129.4 (CH), 128.6 (CH), 128.5 (2 x CH), 127.0 (CH), 126.2 (2 x CH), 119.7 (CH), 113.3 (CH), 111.3 (CH), 55.2 (CH_3), 42.6 (CH), 21.2 (CH_3). Data consistent with literature.[345]

1-Methoxy-3-[(3*Z*)-4-phenylbut-3-en-2-yl]benzene and 1-methoxy-3-[(3*E*)-4-phenylbut-3-en-2-yl]benzene 4.117[345]



1 : 1

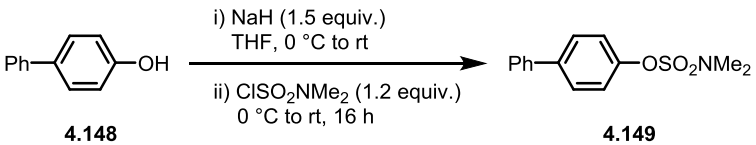


General procedure A (method 1) was applied to 3-methoxystyrene **4.71** (97 µL, 0.7 mmol), $FeCl_2 \cdot 4H_2O$ (0.7 mg, 0.005 mmol), TMEDA (0.5 µL, 0.005 mmol), ethylmagnesium bromide (3 M in THF, 0.35 mL, 1.1 mmol) and *α*-bromostyrene (0.15 mL, 1.1 mmol). The crude product was purified by flash chromatography (pentane→pentane/Et_2O 99:1) to give alkene **4.117** (107 mg, 64%) as a 1:1 inseparable mixture of cis/trans isomers and a colourless oil. R_f 0.48 (pet. ether/Et_2O 99:1). Data consistent with literature.[345]

Cis: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.18 (6H, m, Ar**H**), 6.90 (1H, d, *J* = 7.5 Hz, Ar**H**), 6.86-6.84 (1H, m, Ar**H**), 6.80-6.75 (1H, m, Ar**H**), 6.51 (1H, d, *J* = 11.5 Hz, C**H**Ph), 5.84 (1H, dd, *J* = 11.5, 10.5 Hz, C**H**=CHPh), 4.01 (1H, qd, *J* = 10.5, 7.0 Hz, C**H**CH_3), 3.82 (3H, s, OC**H**$_3$), 1.41 (3H, d, *J* = 7.0 Hz, CHC**H**$_3$);^{13}C NMR (125.8 MHz, $CDCl_3$) δ 159.8 (C), 147.9 (C), 137.4 (C), 136.8 (CH), 129.5 (CH), 128.7 (2 x CH), 128.2 (2 x CH) 127.9 (CH), 126.7 (CH), 119.3 (CH), 113.0 (CH), 111.1 (CH), 55.1 (CH_3), 37.8 (CH), 22.8 (CH_3).

Trans: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.18 (6H, m, Ar**H**), 6.90 (1H, d, *J* = 7.5 Hz, Ar**H**), 6.86-6.84 (1H, m, Ar**H**), 6.80-6.75 (1H, m, Ar**H**), 6.44 (1H, d, *J* = 16.0 Hz, C**H**Ph), 6.39 (1H, dd, *J* = 16.0, 6.0 Hz, C**H**=CHPh), 3.82 (3H, s, OC**H**$_3$), 3.64 (1H, quintet, *J* = 7.0 Hz, C**H**CH_3), 1.48 (3H, d, *J* = 7.0 Hz, CHC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 159.7 (C), 147.4 (C), 137.6 (C), 135.0 (CH), 129.4 (CH), 128.6 (CH), 128.5 (2 x CH), 127.0 (CH), 126.2 (2 x CH), 119.7 (CH), 113.3 (CH), 111.3 (CH), 55.2 (CH_3), 42.6 (CH), 21.2 (CH_3).

4-Phenylphenyl-*N*,*N*-dimethylsulfamate 4.149[297]

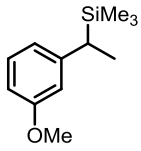


4.148 → **4.149** 37%

To a flask containing NaH (60% dispersion in mineral oil, 350 mg, 8.8 mmol) at 0 °C under nitrogen was added dropwise a solution of 4-phenylphenol **4.148** (990 mg, 5.8 mmol) in THF (40 mL). The reaction was warmed to rt for 15 min and then cooled to 0 °C. *N*,*N*-Dimethylsulfamoyl chloride (0.75 mL, 7.0 mmol) was added dropwise and the reaction warmed to rt for 16 h. The reaction was quenched with a few drops of water and the solvent removed *in vacuo*. The residue was dissolved in EtOAc (40 mL) and water (40 mL) and the phases separated. The organic phase was washed with 1 M NaOH solution (40 mL) and water (40 mL). The aqueous phases were combined and extracted with EtOAc (3 x 50 mL). The organic phases were combined, washed with brine (200 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash chromatography (pet.

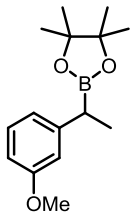
ether/toluene/Et_2O 49.5:49.5:1 → 48:48:4) to give sulfamate **4.149** (596 mg, 37%) as a colourless solid. R_f 0.29 (pet. ether/Et_2O 4:1); m.p. 114-116 °C (lit. 105-107 °C)[346]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63-7.60 (2H, m, Ar**H**), 7.59-7.56 (2H, m, Ar**H**), 7.48-7.44 (2H, m, Ar**H**), 7.40-7.35 (3H, m, Ar**H**), 3.02 (6H, s, N(C**H**$_3$)$_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 149.6 (C), 139.9 (C), 139.9 (C), 128.8 (2 x CH), 128.4 (2 x CH), 127.6 (CH), 127.1 (2 x CH), 122.0 (2 x CH), 38.8 (2 x CH_3). Data consistent with literature.[297]

[1-(3-Methoxyphenyl)ethyl]trimethylsilane 4.152



General procedure A (method 2) was applied to 3-methoxystyrene **4.71** (0.14 mL, 1.0 mmol), $FeCl_2 \cdot 4H_2O$ (1 mg, 0.005 mmol), TMEDA (0.7 µL, 0.005 mmol), ethylmagnesium bromide (3 M in THF, 0.50 mL, 1.5 mmol) and trimethylsilyl chloride (0.20 mL, 1.6 mmol). The crude product was purified by flash chromatography (pet. ether→pet. ether/Et_2O 97:3) to give **4.152** as a colourless oil (173 mg, 97%). R_f 0.32 (pet. ether); IR (film, cm^{-1}) 2953, 2870, 2833, 1599, 1582, 1485, 1456, 1435, 1311, 1248; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (1H, t, *J* = 8.0 Hz, Ar**H**), 6.66 (2H, d, *J* = 8.0 Hz, Ar**H**), 6.62 (1H, s, Ar**H**), 3.81 (3H, s, OC**H**$_3$), 2.17 (1H, q, *J* = 7.5 Hz, C**H**Si(CH$_3$)$_3$), 1.37 (3H, d, *J* = 7.5 Hz, CHC**H**$_3$), −0.03 (9H, s, Si(C**H**$_3$)$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 159.4 (C), 147.8 (C), 128.8 (CH), 119.7 (CH), 113.0 (CH), 109.2 (CH), 55.0 (CH_3), 29.9 (CH), 14.8 (CH_3), −3.3 (3 x CH_3);; HRMS (ES) Exact mass calcd for $C_{12}H_{20}OSiNa$ $[M+Na]^+$: 231.1176, found: 231.1173.

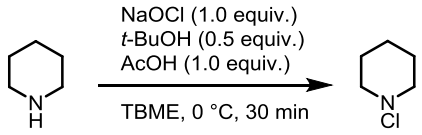
2-(1-(3-Methoxyphenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 4.154[298]



General procedure A (method 2) was applied to 3-methoxystyrene **4.71** (0.14 mL, 1.0 mmol), $FeCl_2 \cdot 4H_2O$ (1 mg, 0.005 mmol), TMEDA (0.7 µL, 0.005 mmol), ethylmagnesium bromide (3 M in THF, 0.50 mL, 1.5 mmol) and pinacolborane (0.23 mL, 1.6 mmol). The crude product was purified by flash chromatography (pet. ether/Et_2O/NEt_3 97:2:1→93:6:1) to give **4.154** as a colourless oil

(129 mg, 45%). R_f 0.52 (9:1 pet. ether/Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (1H, t, *J* = 8.0 Hz, Ar**H**), 6.84-6.81 (1H, m, Ar**H**), 6.81-6.78 (1H, m, Ar**H**), 6.70 (1H, ddd, *J* = 8.0, 2.5, 1.0 Hz, Ar**H**), 3.80 (3H, s, OC**H**$_3$), 2.42 (1H, q, *J* = 7.5 Hz, C**H**CH_3), 1.33 (3H, d, *J* = 7.5 Hz, CHC**H**$_3$), 1.23 (6H, s, $C(C\mathbf{H}_3)_a(CH_3)_bC(C\mathbf{H}_3)_a(CH_3)_b$**)**, 1.22 (6H, s, $C(CH_3)_a(C\mathbf{H}_3)_bC(CH_3)_a(C\mathbf{H}_3)_b$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ (CH resonance not resolved) 159.6 (C), 146.6 (C), 129.1 (CH), 120.3 (CH), 113.5 (CH), 110.5 (CH), 83.3 (2 x C), 55.1 (CH_3), 24.6 (2 x CH_3), 24.6 (2 x CH_3), 17.0 (CH_3); ^{11}B (128 MHz, $CDCl_3$) δ 33.6. Data consistent with literature.[298]

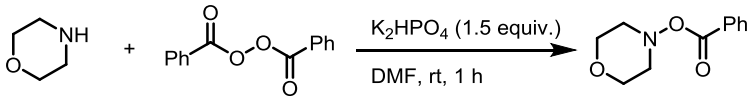
***N*-Chloropiperidine 4.159[300]**



4.158 **4.159** 96%

To a solution of piperidine **4.158** (1.39 mL, 11.7 mmol) and *t*-butanol (0.55 mL, 5.8 mmol) in TBME (30 mL) at 0 °C was slowly added NaOCl (23.5 mL, 11.8 mmol) and acetic acid (0.68 mL, 12.0 mmol). The reaction was stirred at 0°C for 30 min and quenched with water (15 mL). The phases were separated and the aqueous phase extracted with TBME (20 mL). The combined organics were washed with brine (50 mL), dried (Na_2SO_4) and the solvent removed *in vacuo* to give *N*-chloropiperidine **4.159** (1.35 g, 96%) as a pale yellow oil. R_f 0.65 (pet. ether/Et_2O 9:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.77-2.45 (4H, m, $NCl(C\mathbf{H}_2)_2$), 1.77-1.66 (4H, m, $NCl(CH_2)_2(C\mathbf{H}_2)_2$), 1.64-1.17 (2H, m, $NCl(CH_2)_2(CH_2)_2C\mathbf{H}_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 63.9 (2 x CH_2), 27.5 (2 x CH_2), 22.9 (CH_2). Data consistent with literature.[300]

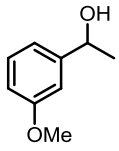
_O_-Benzoyl _N_-hydroxylmorpholine 4.162[347]



4.160 **4.161** **4.162** 81%

To a stirred suspension of benzoyl peroxide **4.161** (70% in water, 2.86 g, 8.26 mmol) and K_2HPO_4 (2.16 g, 12.4 mmol) in DMF (25 mL) was added morpholine **4.160** (0.87 mL, 9.9 mmol). The reaction was stirred for 1 h, quenched with water (25 mL) and stirred vigorously for 30 min. The mixture was extracted with EtOAc (50 mL) and the organic phase washed with sat. aq. $NaHCO_3$ (2 x 50 mL). The aqueous phases were combined and extracted with EtOAc (3 x 50 mL). The organic phases were combined and washed with water (3 x 50 mL), brine (3 x 50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash chromatography (4:1→1:2 pet. ether/EtOAc) to give morpholine **4.162** as a colourless solid (1.40 g, 81%). R_f 0.41 (pet. ether/EtOAc 3:1); m.p. 78-80 °C (lit. 82-84 °C)[347]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (2H, d, *J* = 8.0 Hz, Ar**H**), 7.57 (1H, t, *J* = 7.5 Hz, Ar**H**), 7.45 (2H, t, *J* = 8.0 Hz, Ar**H**), 3.98 (2H, br d, *J* = 11.0 Hz, O(C**H**$_2$)$_a$(CH$_2$)$_b$), 3.87 (2H, br t, *J* = 11.0 Hz, O(CH$_2$)$_a$(C**H**$_2$)$_b$), 3.45 (2H, br d, *J* = 9.5 Hz, N(C**H**$_2$)$_a$(CH$_2$)$_b$), 3.04 (2H, br t, *J* = 9.0 Hz, N(CH$_2$)$_a$(C**H**$_2$)$_b$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 164.5 (C), 133.1 (CH), 129.4 (2 x CH), 129.1 (C), 128.4 (2 x CH), 65.8 (2 x CH_2), 56.9 (2 x CH_2). Data consistent with literature.[347]

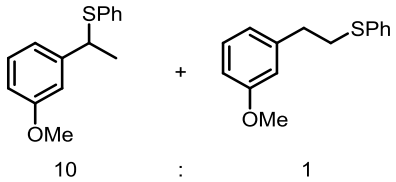
1-(3-Methoxyphenyl)ethan-1-ol 4.170[348]



General procedure A (method 2) was applied to 3-methoxystyrene **4.71** (0.14 mL, 1.0 mmol), $FeCl_2 \cdot 4H_2O$ (1 mg, 0.005 mmol), TMEDA (0.7 µL, 0.005 mmol), ethylmagnesium bromide (3 M in THF, 0.50 mL, 1.5 mmol) and the reaction exposed to air. The crude product was purified by flash chromatography (pet. ether/Et_2O 4:1→1:2) to give **4.170** as a colourless oil (127 mg, 83%). R_f 0.33 (pet. ether/Et_2O 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (1H, t, *J* = 8.0 Hz, Ar**H**), 6.97-6.94 (2H,

m, Ar**H**), 6.83 (1H, ddd, *J* = 8.0, 2.5, 0.5 Hz, Ar**H**), 4.91-4.86 (1H, m, C**H**CH_3), 3.83 (3H, s, OC**H**$_3$), 1.50 (3H, d, *J* = 6.5 Hz, CHC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 159.8 (C), 147.6 (C), 129.5 (CH), 117.7 (CH), 112.9 (CH), 110.9 (CH), 70.3 (CH), 55.2 (CH_3), 25.1 (CH_3). Data consistent with literature.[348]

1-Methoxy-3-[1-(phenylsulfanyl)ethyl]benzene and 1-methoxy-3-[2-(phenylsulfanyl)ethyl]benzene 4.172



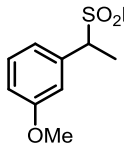
General procedure A (method 2) was applied to 3-methoxystyrene **4.71** (0.14 mL, 1.0 mmol), $FeCl_2 \cdot 4H_2O$ (1 mg, 0.005 mmol), TMEDA (0.7 µL, 0.005 mmol), ethylmagnesium bromide (3 M in THF, 0.50 mL, 1.5 mmol) and the hydromagnesiated intermediate was added to a solution of diphenyl sulfide (349 mg, 1.6 mmol) in THF (2 mL) at −78 °C *via* cannula. The crude product was purified by flash chromatography (pentane→pentane/Et_2O 98.8:1.2) to give a 10:1 *α*:*β* inseparable mixture of **4.172** as a colourless oil (153 mg, 63%). R_f 0.53 (pentane/Et_2O 98:2); IR (film, cm^{-1}) 3057, 2965, 2924, 2833, 1599, 1584, 1481, 1454, 1437, 1315; HRMS (ES) Exact mass calcd for $C_{15}H_{16}OSNa$ $[M+Na]^+$: 267.0814, found: 267.0816.

α: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.29 (2H, m, Ar**H**), 7.26-7.17 (4H, m, Ar**H**), 6.93-6.89 (1H, m, Ar**H**), 6.89 (1H, t, *J* = 2.0 Hz, Ar**H**), 6.77 (1H, ddd, *J* = 8.0, 2.5, 1.0 Hz, Ar**H**), 4.32 (1H, q, *J* = 7.0 Hz, C**H**CH_3), 3.77 (3H, s, OC**H**$_3$), 1.63 (3H, d, *J* = 7.0 Hz, CHC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 159.6 (C), 144.9 (C), 135.2 (C), 132.4 (2 x CH), 129.3 (CH), 128.6 (2 x CH), 127.1 (CH), 119.6 (CH), 112.8 (CH), 112.6 (CH), 55.1 (CH_3), 48.0 (CH), 22.3 (CH_3);

β: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.16 (6H, m, Ar**H**), 6.93-6.73 (3H, m, Ar**H**), 3.80 (3H, s, OC**H**$_3$), 3.21-3.15 (2H, m, C**H**$_2$SPh), 2.92 (2H, dd, 9.0, 6.5 Hz, C**H**$_2$$CH_2$SPh); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 141.8 (C), 136.3 (C), 132.6 (C), 129.5 (CH), 129.2 (2 x CH), 128.9 (2 x CH), 126.0 (CH), 120.8 (CH), 114.3 (CH), 111.7 (CH), 55.1

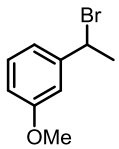
(CH_3), 35.7 (CH_2), 35.0 (CH_2).

1-Methoxy-3-(1-sulfonylethyl)benzene 4.179



General procedure A (method 2) was applied to 3-methoxystyrene **4.71** (0.14 mL, 1.0 mmol), $FeCl_2 \cdot 4H_2O$ (1 mg, 0.5 mol%), TMEDA (0.7 µL, 0.5 mol%), ethylmagnesium bromide (3M in THF, 0.50 mL, 1.5 mmol) and DABSO (384 mg, 1.6 mmol). The hydromagnesiated intermediate was added to a solution of DABSO (1M) at –40 °C. The reaction was quenched with 1 M NaOH (5 mL), the layers were separated and the aqueous layer extracted with Et_2O (3 x 10 mL). The aqueous layer was acidified to pH 1 with 1 M HCl and extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude residue was purified by flash chromatography (EtOAc→EtOAc/ *i*-PrOH 7:3→H_2O/ *i*-PrOH /EtOAc 1:2:7) to yield **4.179** as a colourless solid (35 mg, 17%); R_f 0.15 (H_2O/ *i*-PrOH /EtOAc 1:2:7); m.p. 104 °C (dec.); IR (film, cm^{-1}) 3348, 2924, 2853, 2480, 2243, 2072, 1599, 1489, 1119, 972; ^{1}H NMR (500 MHz, CD_3OD) δ 7.20 (1H, t, *J* = 8.0 Hz, Ar**H**), 6.88-6.83 (2H, m, Ar**H**), 6.78 (1H, dd, *J* = 8.0, 2.5 Hz, Ar**H**), 3.78 (3H, s, OC**H**$_3$), 3.22 (1H, q, *J* = 7.0 Hz, C**H**CH_3), 1.48 (3H, d, *J* = 7.0 Hz, CHC**H**$_3$); ^{13}C NMR (125.8 MHz, CD_3OD) δ 161.0 (C), 141.8 (C), 130.1 (CH), 122.1 (CH), 115.5 (CH), 113.2 (CH), 70.2 (CH), 55.6 (CH_3), 12.7 (CH_3).

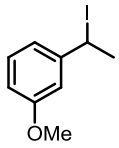
1-(1-Bromoethyl)-3-methoxybenzene 4.182[349]



General procedure A (method 2) was applied to 3-methoxystyrene **4.71** (0.14 mL, 1.0 mmol), $FeCl_2 \cdot 4H_2O$ (1 mg, 0.005 mmol), TMEDA (0.7 µL, 0.005 mmol), ethylmagnesium bromide (3 M in THF, 0.50 mL, 1.5 mmol) and bromine (0.08 mL, 1.6 mmol) at −78 °C to give bromide **4.182** (47% yield by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29-7.25 (1H, m, Ar**H**), 7.05-7.02 (1H, m, Ar**H**), 6.99 (1H, t, J = 2.0 Hz, Ar**H**),

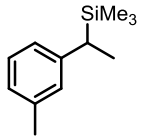
6.84 (1H, ddd, *J* = 8.0, 2.5, 1.0 Hz, Ar**H**), 5.19 (1H, q, *J* = 7.0 Hz, C**H**CH_3), 3.83 (3H, s, OC**H**$_3$), 2.05 (3H, d, *J* = 7.0 Hz, CHC**H**$_3$). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 159.7 (C), 144.7 (C), 129.7 (CH), 119.1 (CH), 113.8 (CH), 112.6 (CH), 55.3 (CH_3), 49.4 (CH), 26.8 (CH_3). Data consistent with literature.[349]

1-(1-Iodoethyl)-3-methoxybenzene 4.184



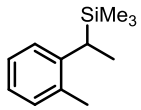
General procedure A (method 2) was applied to 3-methoxystyrene **4.71** (0.14 mL, 1.0 mmol), $FeCl_2 \cdot 4H_2O$ (1 mg, 0.005 mmol), TMEDA (0.7 µL, 0.005 mmol), ethylmagnesium bromide (3 M in THF, 0.50 mL, 1.5 mmol) and iodine (406 mg, 1.6 mmol) to give iodide **4.184** (54% yield by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard). Iodine was added as a solution in anhydrous THF (1 M) at −78 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (1H, t, *J* = 8.0 Hz, Ar**H**), 7.06-7.03 (1H, m, Ar**H**), 6.99 (1H, t, *J* = 2.0 Hz, Ar**H**), 6.80 (1H, ddd, *J* = 8.0, 2.5, 0.5 Hz, Ar**H**), 5.38 (1H, q, *J* = 7.0 Hz, C**H**CH_3), 3.83 (3H, s, OC**H**$_3$), 2.21 (3H, d, *J* = 7.0 Hz, CHC**H**$_3$).

Trimethyl[1-(3-methylphenyl)ethyl]silane 4.192



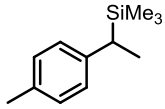
General procedure A (method 1) was applied to 3-methylstyrene **4.189** (91 µL, 0.7 mmol), $FeCl_2 \cdot 4H_2O$ (0.7 mg, 0.007 mmol), TMEDA (0.5 µL, 0.007 mmol), ethylmagnesium bromide (3 M in THF, 0.35 mL, 1.1 mmol) and trimethylsilyl chloride (0.14 mL, 1.1 mmol) to give silane **4.192** (87% yield by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16-7.11 (1H, m, Ar**H**), 6.93-6.89 (1H, m, Ar**H**), 6.88-6.83 (2H, m, Ar**H**), 2.33 (3H, s, ArC**H**$_3$), 2.13 (1H, q, *J* = 7.5 Hz, C**H**CH_3), 1.36 (3H, d, *J* = 7.5 Hz, CHC**H**$_3$), −0.05 (9H, s, Si(C**H**$_3$)$_3$).

Trimethyl[1-(2-methylphenyl)ethyl]silane 4.190



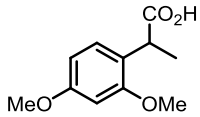
General procedure B was applied to 2-methylstyrene **4.189** (91 µL, 0.7 mmol), $FeCl_2$ (0.9 mg, 0.007 mmol), BIP (3 mg, 0.007 mmol), ethylmagnesium bromide (3 M in THF, 0.35 mL, 1.1 mmol) and trimethylsilyl chloride (0.14 mL, 1.1 mmol) to give silane **4.190** (65% yield by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21-7.10 (2H, m, Ar**H**), 7.06 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.00 (1H, td, *J* = 7.5, 1.0 Hz, Ar**H**), 2.42 (1H, q, *J* = 7.5 Hz, C**H**CH_3), 2.27 (3H, s, ArC**H**$_3$), 1.36 (3H, d, *J* = 7.5 Hz, CHC**H**$_3$), −0.03(9H, s, Si(C**H**$_3$)$_3$).

Trimethyl[1-(4-methylphenyl)ethyl]silane 4.194



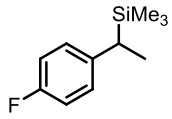
General procedure B was applied to 4-methylstyrene **4.193** (92 µL, 0.7 mmol), $FeCl_2$ (1 mg, 0.007 mmol), BIP (3 mg, 0.007 mmol), ethylmagnesium bromide (3 M in THF, 0.35 mL, 1.1 mmol) and trimethylsilyl chloride (0.14 mL, 1.1 mmol) to give silane **4.194** (88% yield by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.06 (2H, d, *J* = 8.0 Hz, Ar**H**), 6.94 (2H, d, *J* = 8.0 Hz, Ar**H**), 2.31 (3H, s, ArC**H**$_3$), 2.13 (1H, q, *J* = 7.5 Hz, C**H**CH_3), 1.35 (3H, d, *J* = 7.5 Hz, CHC**H**$_3$), −0.05 (9H, s, Si(C**H**$_3$)$_3$).

2-(2,4-Dimethoxyphenyl)propanoic acid 4.201[350]



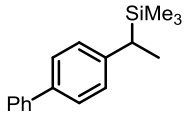
General procedure B was applied to 2,4-dimethoxystyrene **4.198** (92 µL, 0.7 mmol), $FeCl_2$ (1 mg, 0.007 mmol), BIP (3 mg, 0.007 mmol), ethylmagnesium bromide (3 M in THF, 0.35 mL, 1.1 mmol) and carbon dioxide (1 pellet of dry ice) to give carboxylic acid **4.201** (67% yield by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (1H, d, *J* = 8.0 Hz, Ar**H**), 6.51-6.44 (2H, m, Ar**H**), 4.02 (1H, q, *J* = 7.0 Hz, C**H**CH_3), 3.82 (3H, s, OC**H**$_3$), 3.81 (3H, s, OC**H**$_3$), 1.47 (3H, d, *J* = 7.0 Hz, CHC**H**$_3$). Data consistent with literature.[350]

[1-(4-Fluorophenyl)ethyl]trimethylsilane 4.205



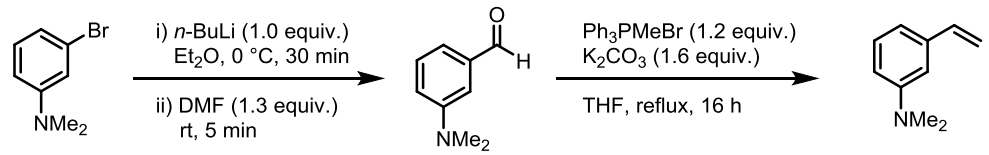
General procedure B was applied to 4-fluorostyrene **4.204** (92 µL, 0.7 mmol), $FeCl_2$ (1 mg, 0.007 mmol), BIP (3 mg, 0.007 mmol), ethylmagnesium bromide (3 M in THF, 0.35 mL, 1.1 mmol) and trimethylsilyl chloride (0.14 mL, 1.1 mmol) to give silane **4.205** (38% yield by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.06-6.90 (4H, m, Ar**H**), 2.15 (1H, q, *J* = 7.5 Hz, C**H**CH_3), 1.34 (3H, d, *J* = 7.5 Hz, CHC**H**$_3$), −0.06 (9H, s, Si(C**H**$_3$)$_3$).

Trimethyl[1-(4-phenylphenyl)ethyl]silane 4.207



General procedure A (method 1) was applied to 4-phenylstyrene **4.206** (126 mg, 0.7 mmol), $FeCl_2 \cdot 4H_2O$ (0.7 mg, 0.007 mmol), TMEDA (0.5 µL, 0.007 mmol), ethylmagnesium bromide (3 M in THF, 0.35 mL, 1.1 mmol) and trimethylsilyl chloride (0.14 mL, 1.1 mmol) to give silane **4.207** (21% yield by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67-7.10 (9H, m, Ar**H**), 2.23 (1H, q, *J* = 7.5 Hz, C**H**CH_3), 1.41 (3H, d, *J* = 7.5 Hz, CHC**H**$_3$), −0.01 (9H, s, Si(C**H**$_3$)$_3$).

3-Ethenyl-*N*,*N*-dimethylaniline 4.214[351]

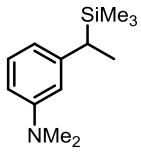


4.212 **4.213** **4.214**
25% over 2 steps

To a stirred solution of bromide **4.212** (1.43 mL, 10.0 mmol) in anhydrous Et_2O (25 mL) at 0 °C under nitrogen was added *n*-BuLi (1.6 M in hexanes, 6.25 mL, 10.0 mmol) dropwise. The reaction was stirred for 30 min and DMF (0.97 mL, 12.5 mmol) added dropwise. The reaction was stirred for 5 min, warmed to room temperature and quenched with 1 N aq. HCl (20 mL). The mixture was neutralised with sat. aq. $NaHCO_3$, the phases separated and the

aqueous phase extracted with Et_2O (3 x 20 mL). The combined organics were washed with sat. aq. $NaHCO_3$ (50 mL), water (50 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue purified by flash chromatography (pet. ether/EtOAc 19:1→4:1) to give aldehyde **4.213** (823 mg, 55%) as a yellow oil. To a stirred suspension of potassium carbonate (1.18 g, 8.54 mmol) and methyltriphenylphosphonium bromide (2.29 g, 6.41 mmol) in anhydrous THF (3 mL) under nitrogen was added aldehyde **4.213** (796 mg, 5.34 mmol) in THF (3 mL) *via* cannula. The reaction was heated at reflux for 16 h, cooled, filtered and the solvent removed *in vacuo*. The residue was dissolved in hot pentane (20 mL), cooled to 0 °C to precipitate triphenylphosphine oxide, filtered and washed with cold pentane (10 mL). The filtrate was concentrated *in vacuo* and purified by flash chromatography (pet. ether/Et_2O 99:1→9:1) to give 3-dimethylaminostyrene **4.214** (357 mg, 45%, 68% brsm) as a colourless oil. R_f 0.60 (pet. ether/Et_2O 9:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (1H, dt, *J* = 8.0, 2.5 Hz, Ar**H**), 6.85 (1H, d, *J* = 7.5 Hz, Ar**H**), 6.80 (1H, s, Ar**H**), 6.73 (1H, ddd, *J* = 17.5, 11.0, 2.5 Hz, C**H**=CH_2), 6.72-6.68 (1H, m, Ar**H**), 5.77 (1H, dd, *J* = 17.5, 2.5 Hz, CH=C**H**$_{trans}$H$_{cis}$), 5.25 (1H, dd, *J* = 11.0, 2.0 Hz, CH=CH$_{trans}$**H**$_{cis}$), 2.99 (3H, s, N(C**H**$_3$)$_a$(CH$_3$)$_b$), 2.99 (3H, s, N(CH$_3$)$_a$(C**H**$_3$)$_b$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 150.9 (C), 138.3 (C), 137.7 (CH), 129.1 (CH), 114.8 (CH), 113.3 (CH_2), 112.4 (CH), 110.6 (CH), 40.6 (2 x CH_3). Data consistent with literature.[351]

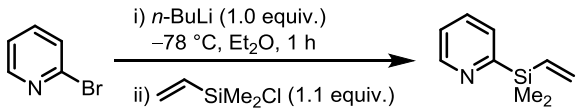
_N_,_N_-Dimethyl-3-[1-(trimethylsilyl)ethyl]aniline 4.215



General procedure A (method 1) was applied to 3-dimethylaminostyrene **4.214** (103 mg, 0.7 mmol), $FeCl_2 \cdot 4H_2O$ (0.7 mg, 0.004 mmol), TMEDA (0.5 µL, 0.004 mmol), ethylmagnesium bromide (3 M in THF, 0.35 mL, 1.1 mmol) and trimethylsilyl chloride (0.14 mL, 1.1 mmol). The crude product was purified by flash chromatography (pet. ether/Et_2O 99:1→95:5), whereupon the product was subjected to dihydroxylation to remove residual styrene. AD-mix-*β* (82 mg, 1.4 g/mmol) was added to a stirred solution of silane and styrene (8.6 mg, 0.059 mmol, 8% by ^{1}H NMR spectroscopy of

crude reaction mixture) in *t*-BuOH/H_2O (1:1 v:v, 4 mL) and the reaction stirred for 5 h. The reaction was quenched with Na_2SO_3 and the mixture diluted with EtOAc (5 mL) and water (5 mL). The phases were separated and the aqueous phase extracted with EtOAc (3 x 10 mL). The combined organics were dried (Na_2SO_4) and the solvent removed *in vacuo*. The residue was purified by flash chromatography (pet. ether/Et_2O 99:1→96:4) to give silane **4.215** as a colourless oil (126 mg, 81%). R_f 0.29 (pet. ether/Et_2O 9:1); IR (film, cm^{-1}) 2953, 2899, 2870, 2799, 1599, 1578, 1499, 1437, 1348, 1246; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (1H, t, *J* = 7.5 Hz, Ar**H**), 6.53 (1H, d, *J* = 8.5 Hz, Ar**H**), 6.48-6.43 (2H, m, Ar**H**), 2.94 (3H, s, $N(C\mathbf{H}_3)_a(CH_3)_b$), 2.94 (3H, s, $N(CH_3)_a(C\mathbf{H}_3)_b$), 2.13 (1H, q, *J* = 7.5 Hz, C**H**CH_3), 1.37 (3H, d, *J* = 7.5 Hz, CHC**H**$_3$), −0.03 (9H, s, $Si(C\mathbf{H}_3)_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 150.5 (C), 146.8 (C), 128.5 (CH), 116.0 (CH), 111.9 (CH), 109.1 (CH), 40.8 (2 x CH_3), 30.1 (CH), 14.9 (CH_3), −3.2 (3 x CH_3); HRMS (ES) Exact mass calcd for $C_{13}H_{23}ONSiNa$ $[M+Na]^+$: 244.1492, found: 244.1492.

Dimethyl(2-pyridinyl)(vinyl)silane 4.216[308]

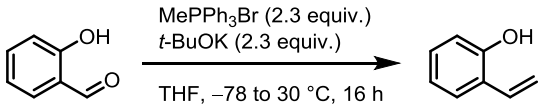


4.219 **4.216** 48%

To a stirred solution of 2-bromopyridine **4.219** (1.2 mL, 13 mmol) in anhydrous Et_2O (50 mL) at −78°C under nitrogen was added *n*-BuLi (1.6 M in hexanes, 7.6 mL, 12 mmol) dropwise. The reaction was stirred at −78°C for 1 h and chlorodimethyl(vinyl)silane (1.8 mL, 13 mmol) added. The reaction was stirred at room temperature for 3 h and quenched with sat. aq. $NaHCO_3$ solution (50 mL). The phases were separated and the aqueous phase extracted with Et_2O (3 x 50 mL). The combined organics were dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude silane was purified by fractional distillation ((b.p. 94 °C/23 mmHg, lit.,[308] 80-84 °C/14 mmHg) to give silane **4.216** (957 mg, 48%) as a pale yellow oil. R_f 0.79 (4:1 pet. ether/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ

8.79 (1H, d, *J* = 5.0 Hz, Ar**H**), 7.58 (1H, t, *J* = 7.5 Hz, Ar**H**), 7.51 (1H, d, *J* = 7.5 Hz, Ar**H**), 7.21-7.17 (1H, m, Ar**H**), 6.35 (1H, dd, *J* = 20.5, 15.5 Hz, $Si(CH_3)_2C\mathbf{H}CH_2$), 6.10 (1H, dd, *J* = 14.5, 3.5 Hz, $Si(CH_3)_2CHC\mathbf{H}_aCH_b$), 5.83 (1H, dd, *J* = 20.5, 3.5 Hz, $Si(CH_3)_2CHCH_aC\mathbf{H}_b$), 0.41 (6H, s, $Si(C\mathbf{H}_3)_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 166.8 (C), 150.3 (CH), 136.9 (CH), 133.9 (CH), 133.4 (CH_2), 129.3 (CH), 122.8 (CH), –3.6 (2 x CH_3). Data consistent with literature.[308]

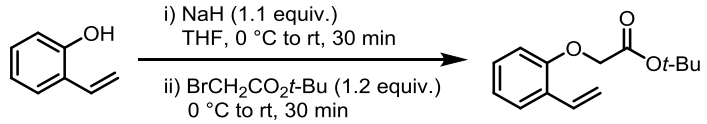
2-Ethenylphenol 4.228[309]



4.227 **4.228** 73%

To a stirred solution of methyltriphenylphosphonim bromide (13.5 g, 37.7 mmol) in anhydrous THF (40 mL) under nitrogen was added a solution of potassium *tert*-butoxide (4.23 g, 37.7 mmol) in THF (40 mL) *via* cannula. The mixture was stirred for 2 h, cooled to −78 °C and salicylaldehyde **4.227** (1.75 mL, 16.5 mmol) added. The reaction was warmed to room temperature slowly and stirred at 30 °C for 16 h. The mixture was quenched with 1 M HCl (50 mL) and the THF removed *in vacuo*. The aqueous phase was extracted with EtOAc (3 x 50 mL), washed with brine (100 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by flash chromatography (pet. ether/Et_2O 19:1→2:1) to give 2-hydroxystyrene **4.228** as a pale yellow oil (1.45 g, 73%). R_f 0.19 (pet. ether/Et_2O 9:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (1H, d, *J* = 7.5 Hz, Ar**H**), 7.16 (1H, dt, *J* = 8.0, 1.5 Hz, Ar**H**), 6.95 (1H, dd, *J* = 17.5, 11.0 Hz, C**H**=CH_2), 6.93 (1H, t, *J* = 7.5 Hz, Ar**H**), 6.81 (1H, dd, *J* = 8.0, 1.0 Hz, Ar**H**), 5.76 (1H, dd, *J* = 17.5, 1.0 Hz, CH=C$\mathbf{H}_{trans}H_{cis}$), 5.38 (1H, dd, *J* = 11.0, 1.5 Hz, CH=$CH_{trans}\mathbf{H}_{cis}$), 5.03-4.97 (1H, br. m, 1H, O**H**); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 152.8 (C), 131.5 (CH), 128.9 (CH), 127.4 (CH), 124.8 (C), 120.9 (CH), 115.9 (CH_2), 115.8 (CH). Data consistent with literature.[309]

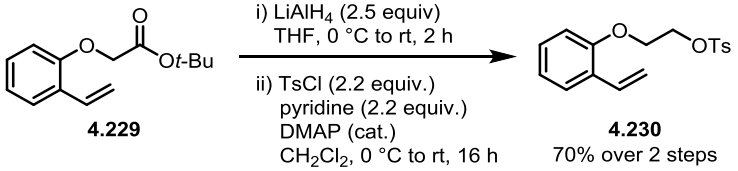
2-(2-Ethenylphenoxy)acetate 4.229



4.228 **4.229** 69%

To a stirred solution of 2-hydroxystyrene **4.228** (500 mg, 4.16 mmol) in anhydrous THF (20 mL) under nitrogen at 0 °C was added sodium hydride (60% in mineral oil, 183 mg, 4.58 mmol). The reaction was warmed to room temperature and stirred for 30 mins. The reaction was cooled to 0 °C, *tert*-butyl bromoacetate (0.74 mL, 4.99 mmol), warmed to room temperature and stirred for 30 mins. The reaction was quenched with water (20 mL), the THF removed *in vacuo* and the aqueous phase extracted with EtOAc (3 x 20 mL). The combined organics were washed with brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude residue was purified by flash chromatography (pet. ether/Et_2O 99:1→95:5) to give *styrene ester* **4.229** (676 mg, 69%) as a colourless oil. R_f 0.39 (pet. ether/Et_2O 95:5); IR (film, cm^{-1}) 2978, 1753 (C=O), 1730, 1626, 1599, 1485, 1454, 1367, 1215, 1152; ^1H NMR (500 MHz, $CDCl_3$) δ 7.50 (1H, dd, *J* = 7.5, 1.5 Hz, Ar**H**), 7.23-7.19 (1H, m, Ar**H**), 7.14 (1H, dd, *J* = 18.0, 11.0 Hz, C**H**=CH_2), 6.98 (1H, t, *J* = 7.5 Hz, Ar**H**), 6.76 (1H, dd, *J* = 8.5, 0.5 Hz, Ar**H**), 5.82 (1H, dd, *J* = 18.0, 1.5 Hz, CH=C$\mathbf{H}_{trans}H_{cis}$), 5.31 (1H, dd, *J* = 11.0, 1.5 Hz, CH=$CH_{trans}\mathbf{H}_{cis}$), 4.56 (2H, s, OC$\mathbf{H}_2$), 1.50 (9H, s, C(C$\mathbf{H}_3)_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 167.9 (C), 155.2 (C), 131.5 (CH), 128.6 (CH), 127.3 (C), 126.9 (CH), 121.5 (CH), 114.9 (CH_2), 112.0 (CH), 82.3 (C), 66.2 (CH_2), 28.0 (3 x CH_3); HRMS (ES) Exact mass calcd for $C_{14}H_{18}O_3Na$ $[M+Na]^+$: 257.1148, found: 257.1148.

2-(2-Ethenylphenoxy)ethyl 4-methylbenzene-1-sulfonate 4.230[352]

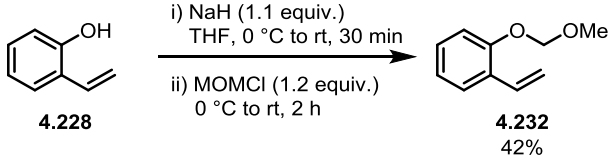


4.229 **4.230** 70% over 2 steps

To a stirred solution of ester **4.229** (200 mg, 0.85 mmol) in anhydrous THF (10 mL) under

nitrogen at 0 °C was added $LiAlH_4$ (81 mg, 2.13 mmol). The reaction was warmed to room temperature and stirred for 2 h. The reaction was carefully quenched at 0 °C with 1 M NaOH (0.1 mL) and water (0.2 mL). The mixture was stirred at 30 min at room temperature and filtered through a pad of celite using Et_2O as eluent. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (pet. ether/Et_2O 3:1→1:2) to give alcohol (131 mg, 94%) as a colourless solid. To a stirred solution of alcohol (121 mg, 0.74 mmol) in anhydrous CH_2Cl_2 (5 mL) at 0 °C under nitrogen was added pyridine (0.13 mL, 1.6 mmol), DMAP (1 crystal, cat.) and tosyl chloride (311 mg, 1.63 mmol). The reaction was warmed to room temperature, stirred for 16 h and quenched with 1N HCl (5 mL). The phases were separated and the aqueous phase extracted with CH_2Cl_2 (3 x 5 mL). The combined organics were washed with sat. aq. $NaHCO_3$ (20 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by flash chromatography (pet. ether/Et_2O 9:1→1:1) to give tosylate **4.230** (175 mg, 74%, 96% brsm) as a colourless solid. R_f 0.32 (pet. ether/Et_2O 3:1); m.p. 58-70 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84-7.82 (2H, m, Ar**H**), 7.47 (1H, dd, *J* = 7.5, 1.5 Hz, Ar**H**), 7.36-7.32 (2H, m, Ar**H**), 7.19 (1H, ddd, *J* = 8.0, 7.5, 1.5 Hz, Ar**H**), 6.98-6.94 (1H, m, Ar**H**), 6.88 (1H, dd, *J* = 18.0, 11.0 Hz, C**H**=CH_2), 6.75 (1H, dd, *J* = 8.5, 1.0 Hz, Ar**H**), 5.70 (1H, dd, *J* = 18.0, 1.5 Hz, CH=C**H**$_{trans}$H$_{cis}$), 5.21 (1H, dd, *J* = 11.0, 1.5 Hz, CH=CH$_{trans}$**H**$_{cis}$), 4.42-4.39 (2H, m, C**H**$_2$OTs), 4.20-4.17 (2H, m, ArOC**H**$_2$), 2.45 (3H, s, C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 155.1 (C), 144.9 (C), 132.9 (C), 131.2 (CH), 129.9 (2 x CH), 128.8 (CH), 127.9 (2 x CH), 127.1 (C), 126.5 (CH), 121.5 (CH), 114.5 (CH_2), 112.1 (CH), 68.1 (CH_2), 65.8 (CH_2), 21.6 (CH_3). Data consistent with literature.[352]

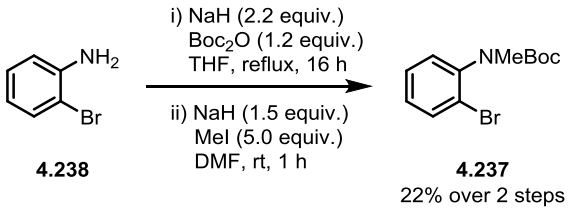
1-Ethenyl-2-(methoxymethoxy)benzene 4.232[353]



4.228 → **4.232** 42%

To 2-hydroxystyrene **4.228** (200 mg, 1.7 mmol) in anhydrous THF (8 mL) at 0 °C under nitrogen was added sodium hydride (60% in mineral oil, 44 mg, 1.8 mmol). The reaction was warmed to room temperature and stirred for 30 min. The reaction was cooled to 0 °C, MOMCl (0.15 mL, 2.0 mmol) added and the reaction stirred at room temperature for 2 h. The reaction was quenched with water (10 mL), the phases separated and the aqueous phase extracted with diethyl ether (3 x 10 mL). The combined organics were washed with 1 M NaOH (40 mL) and water (40 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by flash chromatography (pet. ether/Et_2O 99:1→95:5) to give styrene **4.232** (116 mg, 42%) as a colourless oil. R_f 0.21 (pet. ether/Et_2O 99:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (1H, d, *J* = 7.5 Hz, Ar**H**), 7.23 (1H, t, *J* = 8.0 Hz, Ar**H**), 7.11 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.10 (1H, dd, *J* = 17.5, 11.5 Hz, C**H**=CH_2), 7.01 (1H, t, *J* = 7.5 Hz, Ar**H**), 5.76 (1H, d, *J* = 18.0 Hz, CH=C**H**$_{trans}$H$_{cis}$), 5.29 (1H, d, *J* = 11.0 Hz, CH=CH$_{trans}$**H**$_{cis}$), 5.23 (2H, s, OC**H**$_2$), 3.51 (3H, s, OC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 154.4 (C), 131.5 (CH), 128.8 (CH), 127.6 (C), 126.4 (CH), 121.9 (CH), 114.8 (CH), 114.5 (CH_2), 94.7 (CH_2), 56.1 (CH_3). Data consistent with literature.[353]

_N_-(2-bromophenyl)-_N_-methylcarbamate 4.237[354]



4.238 **4.237** 22% over 2 steps

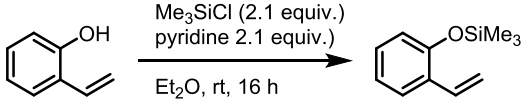
To a solution of sodium hydride (60% in mineral oil, 512 mg, 12.8 mmol) in anhydrous THF (75 mL) under nitrogen was added 2-bromoaniline **4.238** (1.32 mL, 11.6 mmol). The mixture was heated to reflux for 1 h, cooled to room temperature and Boc_2O (3.03 g, 13.9 mmol) added. The mixture was stirred for 30 min at room temperature, a second portion of sodium hydride (60% in mineral oil, 512 mg, 12.8 mmol) added, and heated to reflux for 16 h. The reaction was cooled to room temperature, quenched with water (75 mL) and the THF

removed *in vacuo*. The aqueous phase was extracted with Et_2O (3 x 50 mL) and the combined organics washed with sat. aq. NH_4Cl (50 mL), sat. aq. $NaHCO_3$ (50 mL) and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue purified by flash chromatography (pet. ether/Et_2O 19:1→9:1) to give Boc protected aniline (972 mg, 31%) as a colourless oil. To a solution of carbamate (972 mg, 3.57 mmol) in anhydrous DMF (20 mL) under nitrogen was added sodium hydride (60% in mineral oil, 214 mg, 5.36 mmol) and methyl iodide (1.11 mL, 17.9 mmol). The mixture was stirred for 1 h, quenched with water (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organics were washed with 1:1 H_2O/brine (3 x 50 mL), dried (Na_2SO_4) and the solvent removed *in vacuo*. The crude residue was purified by flash chromatography (pet. ether/Et_2O 19:1→4:1) to give bromide **4.267** (731 mg, 72%) as a colourless oil and 1:3 mixture of rotamers. R_f 0.29 (pet. ether/Et_2O 9:1).

Major rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.31 (1H, t, *J* = 7.0 Hz, Ar**H**), 7.23 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.14 (1H, t, *J* = 7.0 Hz, Ar**H**), 3.16 (3H, s, NC**H**$_3$), 1.35 (9H, s, C(C**H**$_3$)$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 154.5 (C), 142.6 (C), 133.1 (CH), 129.4 (CH), 128.5 (CH), 128.2 (CH), 123.2 (C), 80.1 (CH_3), 36.3 (C), 28.1 (3 x CH_3).

Minor rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.31 (2H, t, *J* = 7.0 Hz, Ar**H**), 7.14 (1H, t, *J* = 7.0 Hz, Ar**H**), 3.16 (3H, s, NC**H**$_3$), 1.54 (9H, s, C(C**H**$_3$)$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ (2 x C resonances not resolved) 133.4 (CH), 129.9 (CH), 128.7 (CH), 128.5 (CH), 123.4, (C), 80.5 (CH_3), 37.3 (C), 28.4 (3 x CH_3). Data consistent with literature.[354]

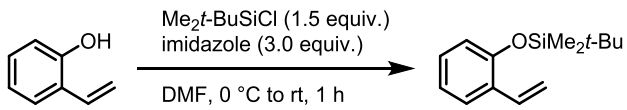
2-Ethenylphenoxytrimethylsilane 4.241[314]



4.228 **4.241** 49%

To a stirred solution of 2-hydroxystyrene **4.228** (200 mg, 1.66 mmol) in anhydrous diethyl ether (5 mL) under nitrogen was added pyridine (0.28 mL, 3.45 mmol) and trimethylsilyl chloride (0.44 mL, 3.45 mmol). The reaction was stirred for 16 h and quenched with water (5 mL). The phases were separated and the aqueous phase extracted with EtOAc (3 x 5 mL). The combined organics were washed with brine (20 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by flash chromatography (pet. ether/Et_2O 99:1→98:2) to give TMS protected alcohol **4.241** (155 mg, 49%) as a colourless oil. R_f 0.84 (pet. ether/Et_2O 19:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (1H, d, *J* = 7.5 Hz, Ar**H**), 7.18-7.13 (1H, m, Ar**H**), 7.00 (1H, dd, *J* = 18.0, 11.0 Hz, C**H**=CH_2), 6.97-6.94 (1H, m, Ar**H**), 6.81 (1H, d, *J* = 8.0 Hz, Ar**H**), 5.73 (1H, td, *J* = 18.0, 1.5 Hz, CH=C$\mathbf{H}_{trans}H_{cis}$), 5.25 (1H, td, *J* = 11.0, 1.0 Hz, CH=$CH_{trans}\mathbf{H}_{cis}$), 0.29 (9H, s, Si(C$\mathbf{H}_3)_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 152.7 (C), 132.1 (CH), 129.0 (C) 128.6 (CH), 126.3 (CH), 121.5 (CH), 119.8 (CH), 113.8 (CH_2), 0.4 (3 x CH_3). Data consistent with literature.[314]

tert-Butyl(2-ethenylphenoxy)dimethylsilane 4.242[315]

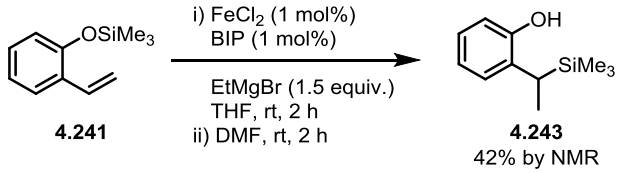


4.228 **4.242** 75%

To a solution of 2-hydroxystyrene **4.228** (500 mg, 4.16 mmol) in anhydrous DMF (5 mL) under nitrogen were added imidazole (849 mg, 12.5 mmol) and TBSCl (940 mg, 6.24 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 1 h. The reaction was diluted with water (10 mL), the phases separated and the aqueous phase extracted with EtOAc (3 x 10 mL). The combined organics were washed with 1:1 water/brine (3 x 10 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by flash chromatography (pentane) to give TBS-protected alcohol **4.242** as a colourless oil (727 mg, 75%). R_f 0.52 (pentane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (1H, dd, *J* = 7.5, 1.5 Hz, Ar**H**), 7.15 (1H, td, *J* = 7.5, 1.5 Hz, Ar**H**), 7.07 (1H, dd, *J* = 18.0, 11.0 Hz, C**H**=CH_2), 6.95 (1H, t,

J = 7.5 Hz, Ar**H**), 6.81 (1H, d, *J* = 8.0 Hz, Ar**H**), 5.69 (1H, dd, *J* = 18.0, 1.0 Hz, CH=C**H**$_{trans}$H$_{cis}$), 5.24 (1H, dd, *J* = 11.0, 1.0 Hz, CH=CH$_{trans}$**H**$_{cis}$), 1.04 (9H, s, Si(CH$_3$)$_2$C(C**H**$_3$)$_3$), 0.23 (6H, s, Si(C**H**$_3$)$_2$C(CH$_3$)$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 152.9 (C), 132.0 (CH), 129.1 (C), 128.6 (CH), 126.0 (CH), 121.3 (CH), 119.6 (CH), 113.6 (CH_2), 25.8 (3 x CH_3), 18.3 (C), -4.2 (CH_3). Data consistent with literature.[315]

2-[1-(Trimethylsilyl)ethyl]phenol 4.243[355]



4.241 **4.243** 42% by NMR

To a solution of $FeCl_2$ (0.3 mg, 0.003 mmol) and BIP (1 mg, 0.003 mmol) in anhydrous THF (2.5 mL) was added TMS-protected alcohol **4.241** (52 mg, 0.27 mmol) and ethylmagnesium bromide (3 M in THF, 0.14 mL, 0.41 mmol) dropwise. The reaction was stirred for 2 h and DMF (33 µL, 0.43 mmol) added. The reaction was stirred for a further 2 h and quenched with aqueous sulphate buffer solution (5 mL). The phases were separated and the aqueous phase extracted with Et_2O (3 x 5 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash chromatography (pet. ether/Et_2O 99:1→93:7) to give alcohol **4.243** (23%, 42% yield by NMR) as a colourless oil. R_f 0.25 (pet. ether/Et_2O 9:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05 (1H, dd, *J* = 7.5, 1.5 Hz, Ar**H**), 6.98 (1H, dt, *J* = 7.5, 1.5 Hz, Ar**H**), 6.90 (1H, *J* = 7.5m 1.0 Hz, Ar**H**), 6.72 (1H, dd, *J* = 8.0, 1.0 Hz, Ar**H**), 4.56 (1H, br s, O**H**), 2.55 (1H, q, *J* = 7.5 Hz, C**H**CH$_3$), 1.36 (3H, d, *J* = 7.5 Hz, CHC**H**$_3$), −0.02 (9H, s, Si(C**H**$_3$)$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 152.1 (C), 132.4 (C), 127.4 (CH), 124.9 (CH), 120.8 (CH), 114.8 (CH), 21.1 (CH), 14.6 (CH_3), −3.2 (3 x CH_3). Data consistent with literature.[355]

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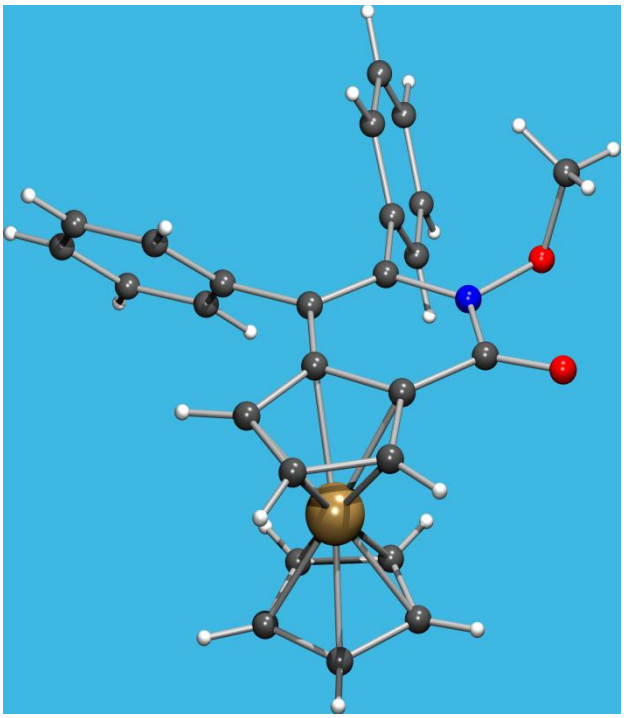
X-ray data for **3.91** and **3.118** is presented below.

Crystal Structure Service
School of Chemistry
The University of Edinburgh

Your code: **3.91** **Our code**: hl3004



Comment

Compound **3.91** was provided as multiple clusters of dark red crystals from which a single piece was broken off and found to be suitable for X-ray diffraction, yielding structure HL3004.

The asymmetric unit of HL3004 is shown in Figure 1. All H atoms were located in a difference Fourier map and are freely refined. Dihedral angles between the central ring and the phenyl and methoxy substituents are 56.34(9)° (C15 to C20); 75.57(4)° (C21 to C26); 85.43(7)° (methoxy).

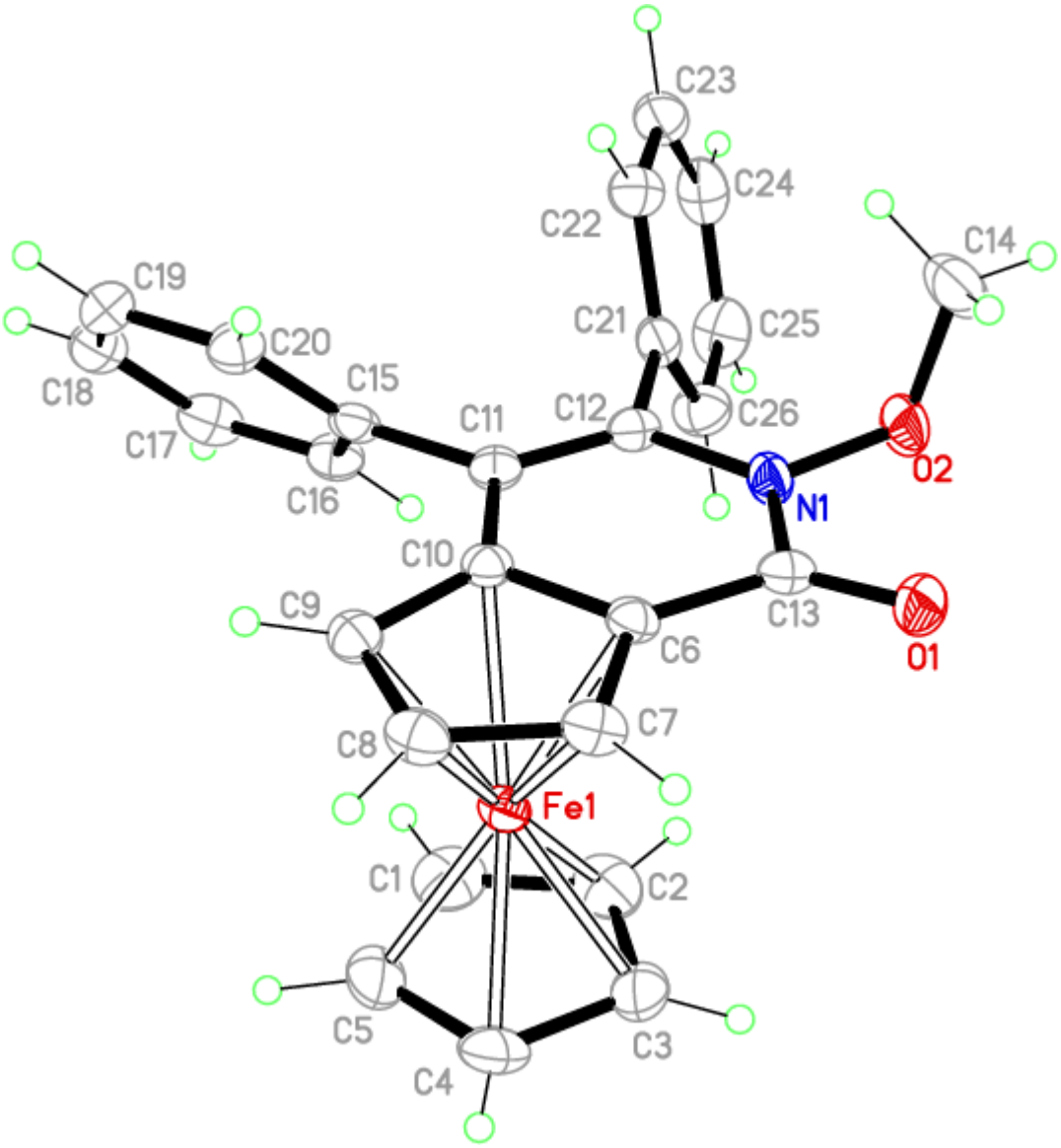


Figure 1. The asymmetric unit of hl3004, with displacement ellipsoids at the 70% probability level.

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References:

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Table 1. Crystal data and structure refinement for hl3004.

Identification code	hl3004	
Chemical formula (moiety)	$C_{26}H_{21}FeNO_2$	
Chemical formula (total)	$C_{26}H_{21}FeNO_2$	
Formula weight	435.29	
Temperature	120(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	triclinic, P -1	
Unit cell parameters	a = 8.8593(4) Å	α = 115.023(4)°
	b = 11.4046(5) Å	β = 101.329(4)°
	c = 11.4216(5) Å	γ = 99.880(4)°
Cell volume	982.29(8) $Å^3$	
Z	2	
Calculated density	1.472 g/cm^3	
Absorption coefficient μ	0.791 mm^{-1}	
F(000)	452	
Crystal colour and size	red, 0.270 × 0.190 × 0.060 mm^3	
Reflections for cell refinement	9883 (θ range 3.2 to 29.6°)	
Data collection method	Agilent Technologies SuperNova ω scans	
θ range for data collection	3.2 to 29.6°	
Index ranges	h −11 to 11, k −15 to 15, l −14 to 15	
Completeness to θ = 25.2°	99.7 %	
Reflections collected	17581	
Independent reflections	4929 (R_{int} = 0.0297)	
Reflections with $F^2>2\sigma$	4422	
Absorption correction	gaussian	
Min. and max. transmission	0.934 and 0.985	
Structure solution	charge-flipping	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4929 / 0 / 355	
Final R indices [$F^2>2\sigma$]	R1 = 0.0327, wR2 = 0.0718	
R indices (all data)	R1 = 0.0378, wR2 = 0.0749	
Goodness-of-fit on F^2	1.078	
Extinction coefficient	0	
Largest and mean shift/su	0.001 and 0.000	
Largest diff. peak and hole	0.40 and −0.34 e $Å^{-3}$	

Table 2. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) for hl3004. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
Fe(1)	0.78070(3)	0.63583(2)	0.91918(2)	0.01223(7)
O(1)	0.32945(14)	0.60937(12)	0.90673(12)	0.0177(2)
O(2)	0.29865(14)	0.79984(12)	0.83611(12)	0.0181(2)
N(1)	0.41729(15)	0.73553(13)	0.80871(13)	0.0133(3)
C(1)	0.9560(2)	0.81718(18)	1.01155(18)	0.0228(4)
C(2)	0.8321(2)	0.82670(18)	1.07497(18)	0.0225(4)
C(3)	0.8219(2)	0.73113(19)	1.12412(17)	0.0216(4)
C(4)	0.9388(2)	0.66254(19)	1.09071(17)	0.0217(4)
C(5)	1.0224(2)	0.71582(19)	1.02155(17)	0.0224(4)
C(6)	0.54365(18)	0.57083(15)	0.81099(15)	0.0123(3)
C(7)	0.58833(19)	0.46806(16)	0.83807(16)	0.0148(3)
C(8)	0.71043(19)	0.43499(16)	0.77780(16)	0.0158(3)
C(9)	0.74479(19)	0.51762(16)	0.71531(16)	0.0138(3)
C(10)	0.63957(18)	0.60184(15)	0.73422(15)	0.0116(3)
C(11)	0.62153(18)	0.70678(15)	0.69703(15)	0.0120(3)
C(12)	0.51065(18)	0.77102(15)	0.73512(15)	0.0127(3)
C(13)	0.42276(18)	0.63736(16)	0.84959(15)	0.0136(3)
C(14)	0.1485(2)	0.7177(2)	0.7309(2)	0.0250(4)
C(15)	0.72641(18)	0.74157(16)	0.62225(15)	0.0123(3)
C(16)	0.82314(19)	0.87315(16)	0.67237(17)	0.0153(3)
C(17)	0.9235(2)	0.90206(18)	0.60255(18)	0.0185(3)
C(18)	0.9278(2)	0.80104(18)	0.48181(17)	0.0189(3)
C(19)	0.8318(2)	0.67022(18)	0.43086(17)	0.0179(3)
C(20)	0.73321(19)	0.64032(17)	0.50110(16)	0.0156(3)
C(21)	0.47736(18)	0.88225(16)	0.70798(16)	0.0133(3)
C(22)	0.3911(2)	0.85385(17)	0.57885(17)	0.0164(3)
C(23)	0.3573(2)	0.95722(18)	0.55397(18)	0.0192(3)
C(24)	0.4123(2)	1.08961(18)	0.65736(19)	0.0210(4)
C(25)	0.5002(2)	1.11860(18)	0.78548(19)	0.0223(4)
C(26)	0.5318(2)	1.01514(17)	0.81141(18)	0.0189(3)

Table 3. Bond lengths [Å] and angles [°] for hl3004.

Fe(1)–C(1)	2.0519(17)	Fe(1)–C(2)	2.0437(18)
Fe(1)–C(3)	2.0419(17)	Fe(1)–C(4)	2.0405(17)
Fe(1)–C(5)	2.0560(17)	Fe(1)–C(6)	2.0392(15)
Fe(1)–C(7)	2.0457(16)	Fe(1)–C(8)	2.0562(16)
Fe(1)–C(9)	2.0608(16)	Fe(1)–C(10)	2.0688(15)
O(1)–C(13)	1.2284(19)	O(2)–N(1)	1.3929(16)
O(2)–C(14)	1.443(2)	N(1)–C(12)	1.4143(19)
N(1)–C(13)	1.388(2)	C(1)–H(1)	0.95(2)
C(1)–C(2)	1.424(3)	C(1)–C(5)	1.419(3)
C(2)–H(2)	0.96(2)	C(2)–C(3)	1.420(3)
C(3)–H(3)	0.94(2)	C(3)–C(4)	1.418(3)
C(4)–H(4)	0.94(2)	C(4)–C(5)	1.422(3)
C(5)–H(5)	0.94(2)	C(6)–C(7)	1.430(2)
C(6)–C(10)	1.438(2)	C(6)–C(13)	1.449(2)
C(7)–H(7)	0.96(2)	C(7)–C(8)	1.414(2)
C(8)–H(8)	0.996(19)	C(8)–C(9)	1.430(2)
C(9)–H(9)	0.954(19)	C(9)–C(10)	1.431(2)
C(10)–C(11)	1.452(2)	C(11)–C(12)	1.355(2)
C(11)–C(15)	1.491(2)	C(12)–C(21)	1.489(2)
C(14)–H(14A)	0.97(2)	C(14)–H(14B)	0.94(2)
C(14)–H(14C)	1.01(2)	C(15)–C(16)	1.398(2)
C(15)–C(20)	1.399(2)	C(16)–H(16)	0.975(19)
C(16)–C(17)	1.391(2)	C(17)–H(17)	0.95(2)
C(17)–C(18)	1.386(3)	C(18)–H(18)	0.94(2)
C(18)–C(19)	1.387(2)	C(19)–H(19)	0.92(2)
C(19)–C(20)	1.388(2)	C(20)–H(20)	0.971(18)
C(21)–C(22)	1.390(2)	C(21)–C(26)	1.391(2)
C(22)–H(22)	0.95(2)	C(22)–C(23)	1.390(2)
C(23)–H(23)	0.95(2)	C(23)–C(24)	1.387(3)
C(24)–H(24)	0.95(2)	C(24)–C(25)	1.383(3)
C(25)–H(25)	0.94(2)	C(25)–C(26)	1.391(2)
C(26)–H(26)	0.93(2)		

C(1)–Fe(1)–C(2)	40.69(7)	C(1)–Fe(1)–C(3)	68.39(7)
C(1)–Fe(1)–C(4)	68.18(8)	C(1)–Fe(1)–C(5)	40.42(7)
C(1)–Fe(1)–C(6)	134.47(7)	C(1)–Fe(1)–C(7)	173.02(7)
C(1)–Fe(1)–C(8)	146.54(7)	C(1)–Fe(1)–C(9)	115.97(7)
C(1)–Fe(1)–C(10)	110.70(7)	C(2)–Fe(1)–C(3)	40.66(8)
C(2)–Fe(1)–C(4)	68.30(8)	C(2)–Fe(1)–C(5)	68.29(7)
C(2)–Fe(1)–C(6)	109.43(7)	C(2)–Fe(1)–C(7)	132.64(7)
C(2)–Fe(1)–C(8)	171.71(7)	C(2)–Fe(1)–C(9)	146.70(7)
C(2)–Fe(1)–C(10)	115.38(7)	C(3)–Fe(1)–C(4)	40.65(7)
C(3)–Fe(1)–C(5)	68.41(7)	C(3)–Fe(1)–C(6)	113.66(7)
C(3)–Fe(1)–C(7)	107.59(7)	C(3)–Fe(1)–C(8)	132.28(7)
C(3)–Fe(1)–C(9)	172.25(7)	C(3)–Fe(1)–C(10)	145.57(7)
C(4)–Fe(1)–C(5)	40.63(7)	C(4)–Fe(1)–C(6)	144.30(7)
C(4)–Fe(1)–C(7)	112.85(7)	C(4)–Fe(1)–C(8)	108.92(7)
C(4)–Fe(1)–C(9)	133.55(7)	C(4)–Fe(1)–C(10)	173.47(7)

C(5)–Fe(1)–C(6)	174.17(7)	C(5)–Fe(1)–C(7)	144.48(7)
C(5)–Fe(1)–C(8)	115.11(7)	C(5)–Fe(1)–C(9)	110.31(7)
C(5)–Fe(1)–C(10)	134.48(7)	C(6)–Fe(1)–C(7)	40.97(6)
C(6)–Fe(1)–C(8)	67.93(6)	C(6)–Fe(1)–C(9)	68.41(6)
C(6)–Fe(1)–C(10)	40.97(6)	C(7)–Fe(1)–C(8)	40.33(7)
C(7)–Fe(1)–C(9)	68.72(6)	C(7)–Fe(1)–C(10)	69.10(6)
C(8)–Fe(1)–C(9)	40.66(6)	C(8)–Fe(1)–C(10)	68.22(6)
C(9)–Fe(1)–C(10)	40.56(6)	N(1)–O(2)–C(14)	109.27(13)
O(2)–N(1)–C(12)	116.66(12)	O(2)–N(1)–C(13)	115.66(12)
C(12)–N(1)–C(13)	127.53(13)	Fe(1)–C(1)–H(1)	124.1(13)
Fe(1)–C(1)–C(2)	69.35(10)	Fe(1)–C(1)–C(5)	69.95(10)
H(1)–C(1)–C(2)	124.9(13)	H(1)–C(1)–C(5)	127.0(13)
C(2)–C(1)–C(5)	108.08(16)	Fe(1)–C(2)–C(1)	69.97(10)
Fe(1)–C(2)–H(2)	125.1(13)	Fe(1)–C(2)–C(3)	69.60(10)
C(1)–C(2)–H(2)	124.0(12)	C(1)–C(2)–C(3)	108.03(16)
H(2)–C(2)–C(3)	127.9(12)	Fe(1)–C(3)–C(2)	69.74(10)
Fe(1)–C(3)–H(3)	124.6(13)	Fe(1)–C(3)–C(4)	69.62(10)
C(2)–C(3)–H(3)	126.7(13)	C(2)–C(3)–C(4)	107.81(16)
H(3)–C(3)–C(4)	125.5(13)	Fe(1)–C(4)–C(3)	69.73(10)
Fe(1)–C(4)–H(4)	125.5(13)	Fe(1)–C(4)–C(5)	70.27(10)
C(3)–C(4)–H(4)	125.1(12)	C(3)–C(4)–C(5)	108.41(16)
H(4)–C(4)–C(5)	126.5(12)	Fe(1)–C(5)–C(1)	69.64(10)
Fe(1)–C(5)–C(4)	69.10(10)	Fe(1)–C(5)–H(5)	125.0(12)
C(1)–C(5)–C(4)	107.67(16)	C(1)–C(5)–H(5)	124.1(12)
C(4)–C(5)–H(5)	128.2(12)	Fe(1)–C(6)–C(7)	69.76(9)
Fe(1)–C(6)–C(10)	70.62(8)	Fe(1)–C(6)–C(13)	125.99(11)
C(7)–C(6)–C(10)	108.93(14)	C(7)–C(6)–C(13)	128.65(14)
C(10)–C(6)–C(13)	122.42(13)	Fe(1)–C(7)–C(6)	69.27(9)
Fe(1)–C(7)–H(7)	124.0(13)	Fe(1)–C(7)–C(8)	70.24(9)
C(6)–C(7)–H(7)	125.8(12)	C(6)–C(7)–C(8)	107.15(14)
H(7)–C(7)–C(8)	127.0(12)	Fe(1)–C(8)–C(7)	69.44(9)
Fe(1)–C(8)–H(8)	124.7(11)	Fe(1)–C(8)–C(9)	69.84(9)
C(7)–C(8)–H(8)	125.9(11)	C(7)–C(8)–C(9)	109.15(14)
H(8)–C(8)–C(9)	124.9(11)	Fe(1)–C(9)–C(8)	69.50(9)
Fe(1)–C(9)–H(9)	126.8(11)	Fe(1)–C(9)–C(10)	70.02(9)
C(8)–C(9)–H(9)	126.4(11)	C(8)–C(9)–C(10)	107.86(14)
H(9)–C(9)–C(10)	125.7(11)	Fe(1)–C(10)–C(6)	68.41(8)
Fe(1)–C(10)–C(9)	69.42(9)	Fe(1)–C(10)–C(11)	124.67(11)
C(6)–C(10)–C(9)	106.89(13)	C(6)–C(10)–C(11)	120.07(14)
C(9)–C(10)–C(11)	132.98(14)	C(10)–C(11)–C(12)	117.68(14)
C(10)–C(11)–C(15)	119.44(13)	C(12)–C(11)–C(15)	122.86(13)
N(1)–C(12)–C(11)	120.21(13)	N(1)–C(12)–C(21)	114.58(13)
C(11)–C(12)–C(21)	125.20(14)	O(1)–C(13)–N(1)	122.17(14)
O(1)–C(13)–C(6)	125.72(14)	N(1)–C(13)–C(6)	112.04(13)
O(2)–C(14)–H(14A)	113.4(12)	O(2)–C(14)–H(14B)	104.0(14)
O(2)–C(14)–H(14C)	108.7(13)	H(14A)–C(14)–H(14B)	108.7(18)
H(14A)–C(14)–H(14C)	110.9(18)	H(14B)–C(14)–H(14C)	110.9(18)
C(11)–C(15)–C(16)	121.57(14)	C(11)–C(15)–C(20)	119.83(14)
C(16)–C(15)–C(20)	118.57(14)	C(15)–C(16)–H(16)	119.8(11)
C(15)–C(16)–C(17)	120.39(16)	H(16)–C(16)–C(17)	119.8(11)

C(16)–C(17)–H(17)	118.2(13)	C(16)–C(17)–C(18)	120.45(16)
H(17)–C(17)–C(18)	121.3(13)	C(17)–C(18)–H(18)	120.2(12)
C(17)–C(18)–C(19)	119.64(15)	H(18)–C(18)–C(19)	120.1(12)
C(18)–C(19)–H(19)	118.7(12)	C(18)–C(19)–C(20)	120.18(16)
H(19)–C(19)–C(20)	121.1(12)	C(15)–C(20)–C(19)	120.76(15)
C(15)–C(20)–H(20)	118.9(11)	C(19)–C(20)–H(20)	120.3(11)
C(12)–C(21)–C(22)	120.11(14)	C(12)–C(21)–C(26)	120.40(14)
C(22)–C(21)–C(26)	119.49(15)	C(21)–C(22)–H(22)	120.4(11)
C(21)–C(22)–C(23)	120.18(16)	H(22)–C(22)–C(23)	119.4(11)
C(22)–C(23)–H(23)	118.1(12)	C(22)–C(23)–C(24)	120.10(16)
H(23)–C(23)–C(24)	121.8(12)	C(23)–C(24)–H(24)	119.6(13)
C(23)–C(24)–C(25)	119.91(16)	H(24)–C(24)–C(25)	120.4(13)
C(24)–C(25)–H(25)	122.1(13)	C(24)–C(25)–C(26)	120.16(17)
H(25)–C(25)–C(26)	117.7(13)	C(21)–C(26)–C(25)	120.14(16)
C(21)–C(26)–H(26)	120.2(12)	C(25)–C(26)–H(26)	119.6(12)

Table 4. Anisotropic displacement parameters ($Å^2$) for hl3004. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ...+ 2hka^*b^*U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Fe(1)	0.01070(12)	0.01299(12)	0.01189(12)	0.00565(9)	0.00155(8)	0.00349(9)
O(1)	0.0165(6)	0.0237(6)	0.0196(6)	0.0143(5)	0.0088(5)	0.0069(5)
O(2)	0.0171(6)	0.0225(6)	0.0217(6)	0.0120(5)	0.0100(5)	0.0132(5)
N(1)	0.0123(6)	0.0155(6)	0.0159(7)	0.0089(6)	0.0062(5)	0.0071(5)
C(1)	0.0201(9)	0.0180(8)	0.0180(9)	0.0040(7)	–0.0004(7)	–0.0042(7)
C(2)	0.0209(9)	0.0163(8)	0.0183(9)	0.0001(7)	0.0005(7)	0.0051(7)
C(3)	0.0153(8)	0.0299(10)	0.0121(8)	0.0051(7)	0.0025(6)	0.0037(7)
C(4)	0.0184(9)	0.0277(9)	0.0147(8)	0.0091(7)	–0.0017(6)	0.0068(7)
C(5)	0.0123(8)	0.0280(10)	0.0161(8)	0.0035(7)	0.0010(6)	0.0025(7)
C(6)	0.0096(7)	0.0135(7)	0.0122(7)	0.0064(6)	0.0010(6)	0.0015(6)
C(7)	0.0141(8)	0.0131(7)	0.0162(8)	0.0082(7)	0.0018(6)	0.0016(6)
C(8)	0.0162(8)	0.0124(7)	0.0166(8)	0.0061(6)	0.0017(6)	0.0047(6)
C(9)	0.0133(8)	0.0127(7)	0.0123(7)	0.0039(6)	0.0025(6)	0.0035(6)
C(10)	0.0107(7)	0.0118(7)	0.0098(7)	0.0043(6)	0.0012(5)	0.0019(6)
C(11)	0.0126(7)	0.0102(7)	0.0108(7)	0.0044(6)	0.0013(6)	0.0019(6)
C(12)	0.0127(7)	0.0130(7)	0.0111(7)	0.0060(6)	0.0018(6)	0.0019(6)
C(13)	0.0128(7)	0.0145(7)	0.0111(7)	0.0057(6)	0.0005(6)	0.0026(6)
C(14)	0.0144(9)	0.0366(11)	0.0316(11)	0.0222(9)	0.0060(7)	0.0100(8)
C(15)	0.0109(7)	0.0151(7)	0.0125(7)	0.0086(6)	0.0015(6)	0.0041(6)
C(16)	0.0159(8)	0.0139(8)	0.0151(8)	0.0073(7)	0.0021(6)	0.0041(6)
C(17)	0.0158(8)	0.0176(8)	0.0224(9)	0.0131(7)	0.0013(7)	0.0010(7)
C(18)	0.0151(8)	0.0276(9)	0.0204(8)	0.0174(8)	0.0059(7)	0.0044(7)
C(19)	0.0183(8)	0.0217(9)	0.0133(8)	0.0073(7)	0.0053(6)	0.0066(7)
C(20)	0.0155(8)	0.0147(8)	0.0142(8)	0.0061(7)	0.0028(6)	0.0025(6)
C(21)	0.0118(7)	0.0150(7)	0.0166(8)	0.0094(6)	0.0058(6)	0.0053(6)
C(22)	0.0160(8)	0.0159(8)	0.0167(8)	0.0081(7)	0.0041(6)	0.0034(6)
C(23)	0.0175(8)	0.0262(9)	0.0218(9)	0.0173(8)	0.0071(7)	0.0080(7)
C(24)	0.0232(9)	0.0221(9)	0.0318(10)	0.0199(8)	0.0151(8)	0.0130(7)
C(25)	0.0286(10)	0.0143(8)	0.0262(9)	0.0086(8)	0.0125(8)	0.0090(7)
C(26)	0.0211(9)	0.0173(8)	0.0164(8)	0.0067(7)	0.0042(7)	0.0063(7)

Table 5. Hydrogen coordinates and isotropic displacement parameters ($Å^2$) for hl3004.

	x	y	z	U
H(1)	0.984(2)	0.868(2)	0.967(2)	0.027(5)
H(2)	0.768(3)	0.887(2)	1.080(2)	0.025(5)
H(3)	0.749(2)	0.714(2)	1.168(2)	0.025(5)
H(4)	0.957(2)	0.593(2)	1.111(2)	0.022(5)
H(5)	1.105(2)	0.689(2)	0.985(2)	0.021(5)
H(7)	0.545(2)	0.431(2)	0.890(2)	0.026(5)
H(8)	0.768(2)	0.3681(19)	0.7815(19)	0.018(5)
H(9)	0.823(2)	0.5162(18)	0.6679(19)	0.015(5)
H(14A)	0.154(2)	0.700(2)	0.641(2)	0.027(5)
H(14B)	0.077(3)	0.770(2)	0.754(2)	0.034(6)
H(14C)	0.113(3)	0.631(2)	0.735(2)	0.036(6)
H(16)	0.822(2)	0.9445(19)	0.758(2)	0.017(5)
H(17)	0.991(3)	0.991(2)	0.641(2)	0.031(6)
H(18)	0.993(2)	0.8215(19)	0.434(2)	0.020(5)
H(19)	0.835(2)	0.604(2)	0.350(2)	0.020(5)
H(20)	0.668(2)	0.5485(19)	0.4666(18)	0.013(4)
H(22)	0.356(2)	0.764(2)	0.506(2)	0.018(5)
H(23)	0.296(2)	0.934(2)	0.466(2)	0.025(5)
H(24)	0.388(2)	1.159(2)	0.640(2)	0.026(5)
H(25)	0.544(3)	1.207(2)	0.856(2)	0.033(6)
H(26)	0.590(2)	1.0354(19)	0.898(2)	0.017(5)

Table 6. Torsion angles [°] for hl3004.

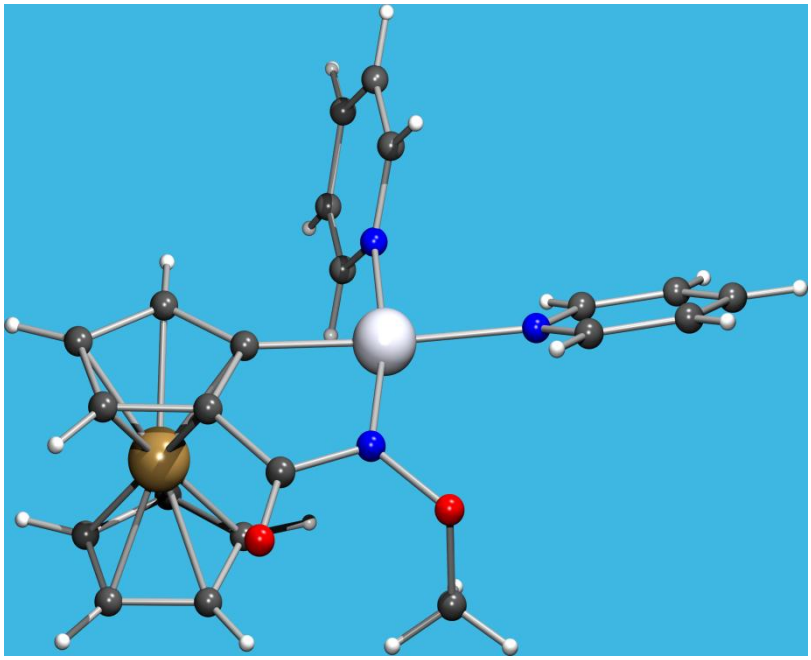
C(14)–O(2)–N(1)–C(12)	93.10(16)	C(14)–O(2)–N(1)–C(13)	–82.88(16)
Fe(1)–C(1)–C(2)–C(3)	59.41(12)	C(5)–C(1)–C(2)–Fe(1)	–59.43(12)
C(5)–C(1)–C(2)–C(3)	0.0(2)	Fe(1)–C(2)–C(3)–C(4)	59.44(12)
C(1)–C(2)–C(3)–Fe(1)	–59.64(12)	C(1)–C(2)–C(3)–C(4)	–0.2(2)
Fe(1)–C(3)–C(4)–C(5)	59.86(12)	C(2)–C(3)–C(4)–Fe(1)	–59.51(12)
C(2)–C(3)–C(4)–C(5)	0.3(2)	Fe(1)–C(1)–C(5)–C(4)	–58.83(12)
C(2)–C(1)–C(5)–Fe(1)	59.06(12)	C(2)–C(1)–C(5)–C(4)	0.23(19)
Fe(1)–C(4)–C(5)–C(1)	59.16(12)	C(3)–C(4)–C(5)–Fe(1)	–59.52(12)
C(3)–C(4)–C(5)–C(1)	–0.36(19)	Fe(1)–C(6)–C(7)–C(8)	–60.32(11)
C(10)–C(6)–C(7)–Fe(1)	59.97(11)	C(10)–C(6)–C(7)–C(8)	–0.35(18)
C(13)–C(6)–C(7)–Fe(1)	–120.47(16)	C(13)–C(6)–C(7)–C(8)	179.21(15)
Fe(1)–C(7)–C(8)–C(9)	–58.68(11)	C(6)–C(7)–C(8)–Fe(1)	59.70(11)
C(6)–C(7)–C(8)–C(9)	1.02(18)	Fe(1)–C(8)–C(9)–C(10)	–59.75(11)
C(7)–C(8)–C(9)–Fe(1)	58.43(11)	C(7)–C(8)–C(9)–C(10)	–1.32(18)
Fe(1)–C(9)–C(10)–C(6)	–58.35(10)	Fe(1)–C(9)–C(10)–C(11)	118.74(18)
C(8)–C(9)–C(10)–Fe(1)	59.42(11)	C(8)–C(9)–C(10)–C(6)	1.07(17)
C(8)–C(9)–C(10)–C(11)	178.16(16)	Fe(1)–C(6)–C(10)–C(9)	58.99(10)
Fe(1)–C(6)–C(10)–C(11)	–118.55(14)	C(7)–C(6)–C(10)–Fe(1)	–59.44(11)
C(7)–C(6)–C(10)–C(9)	–0.45(17)	C(7)–C(6)–C(10)–C(11)	–177.99(13)
C(13)–C(6)–C(10)–Fe(1)	120.97(15)	C(13)–C(6)–C(10)–C(9)	179.95(14)
C(13)–C(6)–C(10)–C(11)	2.4(2)	Fe(1)–C(10)–C(11)–C(12)	–84.42(17)
Fe(1)–C(10)–C(11)–C(15)	94.25(16)	C(6)–C(10)–C(11)–C(12)	–1.1(2)
C(6)–C(10)–C(11)–C(15)	177.56(14)	C(9)–C(10)–C(11)–C(12)	–177.88(16)
C(9)–C(10)–C(11)–C(15)	0.8(3)	C(10)–C(11)–C(12)–N(1)	0.1(2)
C(10)–C(11)–C(12)–C(21)	178.99(14)	C(15)–C(11)–C(12)–N(1)	–178.51(14)
C(15)–C(11)–C(12)–C(21)	0.4(2)	O(2)–N(1)–C(12)–C(11)	–175.82(13)
O(2)–N(1)–C(12)–C(21)	5.19(19)	C(13)–N(1)–C(12)–C(11)	–0.4(2)
C(13)–N(1)–C(12)–C(21)	–179.38(14)	O(2)–N(1)–C(13)–O(1)	–0.3(2)
O(2)–N(1)–C(13)–C(6)	176.97(12)	C(12)–N(1)–C(13)–O(1)	–175.75(15)
C(12)–N(1)–C(13)–C(6)	1.5(2)	Fe(1)–C(6)–C(13)–O(1)	–96.74(18)
Fe(1)–C(6)–C(13)–N(1)	86.12(16)	C(7)–C(6)–C(13)–O(1)	–4.8(3)
C(7)–C(6)–C(13)–N(1)	178.03(15)	C(10)–C(6)–C(13)–O(1)	174.68(15)
C(10)–C(6)–C(13)–N(1)	–2.5(2)	C(10)–C(11)–C(15)–C(16)	–123.38(16)
C(10)–C(11)–C(15)–C(20)	54.5(2)	C(12)–C(11)–C(15)–C(16)	55.2(2)
C(12)–C(11)–C(15)–C(20)	–126.86(17)	C(11)–C(15)–C(16)–C(17)	178.06(14)
C(20)–C(15)–C(16)–C(17)	0.1(2)	C(15)–C(16)–C(17)–C(18)	0.6(2)
C(16)–C(17)–C(18)–C(19)	–0.3(2)	C(17)–C(18)–C(19)–C(20)	–0.7(2)
C(18)–C(19)–C(20)–C(15)	1.4(2)	C(11)–C(15)–C(20)–C(19)	–179.09(14)
C(16)–C(15)–C(20)–C(19)	–1.1(2)	N(1)–C(12)–C(21)–C(22)	–105.61(17)
N(1)–C(12)–C(21)–C(26)	74.25(19)	C(11)–C(12)–C(21)–C(22)	75.5(2)
C(11)–C(12)–C(21)–C(26)	–104.68(19)	C(12)–C(21)–C(22)–C(23)	178.78(15)
C(26)–C(21)–C(22)–C(23)	–1.1(2)	C(21)–C(22)–C(23)–C(24)	1.3(2)
C(22)–C(23)–C(24)–C(25)	–0.3(3)	C(23)–C(24)–C(25)–C(26)	–0.9(3)
C(24)–C(25)–C(26)–C(21)	1.1(3)	C(12)–C(21)–C(26)–C(25)	–179.94(16)
C(22)–C(21)–C(26)–C(25)	–0.1(2)		

Table 7. Hydrogen bonds for hl3004 [Å and °].

D–H...A	d(D–H)	d(H...A)	d(D...A)	<(DHA)

Crystal Structure Service
School of Chemistry
The University of Edinburgh

Your code: **3.118** **Our code**: hl3006



Comment

Compound **3.118** was provided as yellow block crystals suitable for single crystal X-ray diffraction, yielding structure HL3006.

The structure of the metal complex in HL3006 is shown in Figure 1. The structure matches that which was predicted. The compound crystallized as a $CDCl_3$ solvate, which is omitted from the diagram.

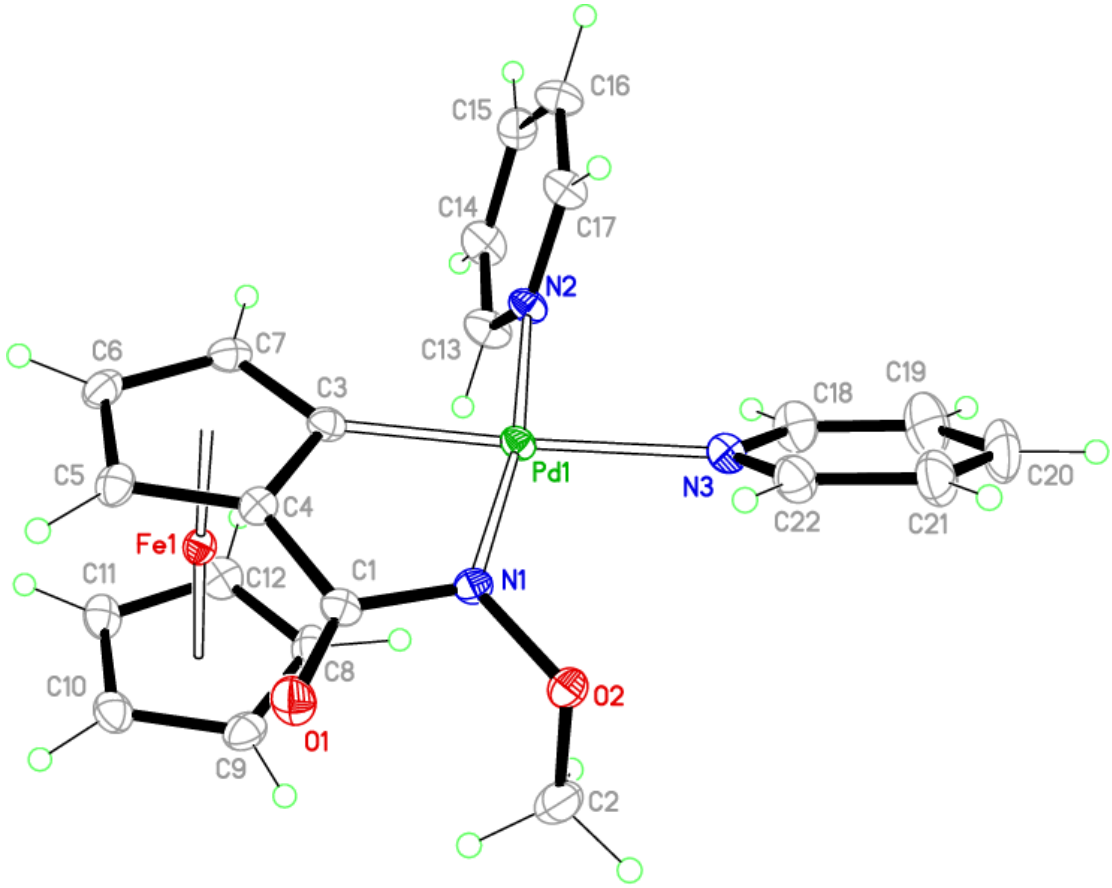


Figure 1. The structure of the metal complex in HL3006. Displacement ellipsoids are at the 50% probability level.

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References:

CRYSALISPRO (data collection, integration and absorption correction)
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SHELXTL (structure refinement and molecular graphics)
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SUPERFLIP (structure solution)
Palatinus L. and Chapuis G. (2007). ***J. Appl. Cryst.*** **40**, 786-790.

Table 1. Crystal data and structure refinement for hl3006.

Identification code	hl3006	
Chemical formula (moiety)	$C_{22}H_{21}FeN_3O_2Pd \cdot CDCl_3$	
Chemical formula (total)	$C_{23}H_{21}Cl_3DFeN_3O_2Pd$	
Formula weight	642.04	
Temperature	120(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	triclinic, P -1	
Unit cell parameters	a = 9.9121(2) Å	α = 94.945(2)°
	b = 10.4629(3) Å	β = 99.282(2)°
	c = 13.1708(3) Å	γ = 113.033(2)°
Cell volume	1223.70(5) $Å^3$	
Z	2	
Calculated density	1.742 g/cm^3	
Absorption coefficient μ	1.681 mm^{-1}	
F(000)	640	
Crystal colour and size	yellow , 0.210 × 0.150 × 0.120 mm^3	
Reflections for cell refinement	15317 (θ range 3.5 to 29.1°)	
Data collection method	Agilent Technologies SuperNova ω scans	
θ range for data collection	2.9 to 29.4°	
Index ranges	h −13 to 12, k −14 to 14, l −18 to 18	
Completeness to θ = 25.2°	99.8 %	
Reflections collected	32923	
Independent reflections	6244 (R_{int} = 0.0509)	
Reflections with $F^2>2\sigma$	5486	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.92492 and 1.00000	
Structure solution	charge-flipping	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6244 / 0 / 299	
Final R indices [$F^2>2\sigma$]	R1 = 0.0295, wR2 = 0.0566	
R indices (all data)	R1 = 0.0370, wR2 = 0.0607	
Goodness-of-fit on F^2	1.030	
Extinction coefficient	0	
Largest and mean shift/su	0.001 and 0.000	
Largest diff. peak and hole	0.84 and −0.83 e $Å^{-3}$	

Table 2. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) for hl3006. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
Pd(1)	0.46017(2)	0.38951(2)	0.33700(2)	0.01253(5)
Fe(1)	0.19777(3)	0.43196(3)	0.13496(2)	0.01312(7)
O(1)	0.00226(16)	0.14441(17)	0.28909(13)	0.0199(3)
O(2)	0.24190(17)	0.08522(16)	0.34145(12)	0.0176(3)
N(1)	0.26090(19)	0.22472(18)	0.32863(14)	0.0140(4)
N(2)	0.63951(19)	0.57310(19)	0.33724(14)	0.0147(4)
N(3)	0.6046(2)	0.3007(2)	0.41023(14)	0.0170(4)
C(1)	0.1311(2)	0.2375(2)	0.29831(16)	0.0138(4)
C(2)	0.2187(3)	0.0056(3)	0.24155(19)	0.0246(5)
C(3)	0.3203(2)	0.4728(2)	0.28517(16)	0.0148(4)
C(4)	0.1664(2)	0.3827(2)	0.27779(16)	0.0135(4)
C(5)	0.0734(3)	0.4516(2)	0.24038(17)	0.0170(4)
C(6)	0.1721(3)	0.5869(2)	0.22443(17)	0.0186(5)
C(7)	0.3231(3)	0.5998(2)	0.25148(17)	0.0175(4)
C(8)	0.2953(3)	0.3364(3)	0.04788(17)	0.0198(5)
C(9)	0.1417(3)	0.2463(3)	0.03891(17)	0.0202(5)
C(10)	0.0538(3)	0.3167(3)	–0.00307(17)	0.0201(5)
C(11)	0.1524(3)	0.4504(3)	–0.01947(17)	0.0196(5)
C(12)	0.3026(3)	0.4637(3)	0.01239(17)	0.0199(5)
C(13)	0.6750(3)	0.6155(3)	0.24764(18)	0.0216(5)
C(14)	0.7867(3)	0.7449(3)	0.24524(19)	0.0230(5)
C(15)	0.8630(3)	0.8363(2)	0.33831(19)	0.0211(5)
C(16)	0.8269(3)	0.7924(2)	0.43012(19)	0.0217(5)
C(17)	0.7162(2)	0.6606(2)	0.42687(17)	0.0181(5)
C(18)	0.7451(3)	0.3360(3)	0.39597(19)	0.0240(5)
C(19)	0.8424(3)	0.2860(3)	0.4478(2)	0.0338(6)
C(20)	0.7938(3)	0.1961(3)	0.5184(2)	0.0323(6)
C(21)	0.6513(3)	0.1615(3)	0.53486(19)	0.0266(5)
C(22)	0.5596(3)	0.2146(3)	0.47961(18)	0.0215(5)
Cl(1)	0.72559(10)	–0.00280(9)	0.04991(7)	0.0544(2)
Cl(2)	0.65163(8)	0.22578(7)	0.12165(6)	0.03766(17)
Cl(3)	0.57197(9)	–0.02199(9)	0.21986(8)	0.0533(2)
C(23)	0.7049(3)	0.0912(3)	0.1583(2)	0.0270(5)
D(23)	0.8037	0.1355	0.2090	0.032

Table 3. Bond lengths [Å] and angles [°] for hl3006.

Pd(1)–N(1)	2.0294(17)	Pd(1)–N(2)	2.0432(18)
Pd(1)–N(3)	2.1426(18)	Pd(1)–C(3)	1.973(2)
Fe(1)–C(3)	2.060(2)	Fe(1)–C(4)	2.033(2)
Fe(1)–C(5)	2.048(2)	Fe(1)–C(6)	2.042(2)
Fe(1)–C(7)	2.048(2)	Fe(1)–C(8)	2.041(2)
Fe(1)–C(9)	2.046(2)	Fe(1)–C(10)	2.058(2)
Fe(1)–C(11)	2.054(2)	Fe(1)–C(12)	2.039(2)
O(1)–C(1)	1.245(3)	O(2)–N(1)	1.425(2)
O(2)–C(2)	1.429(3)	N(1)–C(1)	1.346(3)
N(2)–C(13)	1.347(3)	N(2)–C(17)	1.338(3)
N(3)–C(18)	1.344(3)	N(3)–C(22)	1.344(3)
C(1)–C(4)	1.480(3)	C(2)–H(2A)	0.980
C(2)–H(2B)	0.980	C(2)–H(2C)	0.980
C(3)–C(4)	1.427(3)	C(3)–C(7)	1.428(3)
C(4)–C(5)	1.431(3)	C(5)–H(5)	1.00
C(5)–C(6)	1.428(3)	C(6)–H(6)	1.00
C(6)–C(7)	1.431(3)	C(7)–H(7)	1.00
C(8)–H(8)	1.00	C(8)–C(9)	1.421(3)
C(8)–C(12)	1.429(3)	C(9)–H(9)	1.00
C(9)–C(10)	1.422(3)	C(10)–H(10)	1.00
C(10)–C(11)	1.418(3)	C(11)–H(11)	1.00
C(11)–C(12)	1.428(3)	C(12)–H(12)	1.00
C(13)–H(13)	0.950	C(13)–C(14)	1.381(3)
C(14)–H(14)	0.950	C(14)–C(15)	1.386(3)
C(15)–H(15)	0.950	C(15)–C(16)	1.381(3)
C(16)–H(16)	0.950	C(16)–C(17)	1.378(3)
C(17)–H(17)	0.950	C(18)–H(18)	0.950
C(18)–C(19)	1.383(3)	C(19)–H(19)	0.950
C(19)–C(20)	1.387(4)	C(20)–H(20)	0.950
C(20)–C(21)	1.373(4)	C(21)–H(21)	0.950
C(21)–C(22)	1.384(3)	C(22)–H(22)	0.950
Cl(1)–C(23)	1.748(3)	Cl(2)–C(23)	1.764(2)
Cl(3)–C(23)	1.757(3)	C(23)–D(23)	1.00

N(1)–Pd(1)–N(2)	170.40(7)	N(1)–Pd(1)–N(3)	98.15(7)
N(1)–Pd(1)–C(3)	79.73(8)	N(2)–Pd(1)–N(3)	91.35(7)
N(2)–Pd(1)–C(3)	90.68(8)	N(3)–Pd(1)–C(3)	173.37(8)
C(3)–Fe(1)–C(4)	40.80(8)	C(3)–Fe(1)–C(5)	69.44(9)
C(3)–Fe(1)–C(6)	68.84(9)	C(3)–Fe(1)–C(7)	40.66(8)
C(3)–Fe(1)–C(8)	104.89(9)	C(3)–Fe(1)–C(9)	121.29(9)
C(3)–Fe(1)–C(10)	158.68(9)	C(3)–Fe(1)–C(11)	157.91(9)
C(3)–Fe(1)–C(12)	120.53(9)	C(4)–Fe(1)–C(5)	41.05(8)
C(4)–Fe(1)–C(6)	68.33(9)	C(4)–Fe(1)–C(7)	68.23(9)
C(4)–Fe(1)–C(8)	120.57(9)	C(4)–Fe(1)–C(9)	106.64(9)
C(4)–Fe(1)–C(10)	123.89(9)	C(4)–Fe(1)–C(11)	160.73(9)
C(4)–Fe(1)–C(12)	156.55(9)	C(5)–Fe(1)–C(6)	40.87(9)
C(5)–Fe(1)–C(7)	69.09(9)	C(5)–Fe(1)–C(8)	157.28(9)
C(5)–Fe(1)–C(9)	122.25(9)	C(5)–Fe(1)–C(10)	108.62(9)

C(5)–Fe(1)–C(11)	124.66(9)	C(5)–Fe(1)–C(12)	160.77(9)
C(6)–Fe(1)–C(7)	40.95(9)	C(6)–Fe(1)–C(8)	159.31(10)
C(6)–Fe(1)–C(9)	159.38(10)	C(6)–Fe(1)–C(10)	124.44(9)
C(6)–Fe(1)–C(11)	109.47(9)	C(6)–Fe(1)–C(12)	123.95(9)
C(7)–Fe(1)–C(8)	121.69(9)	C(7)–Fe(1)–C(9)	157.67(9)
C(7)–Fe(1)–C(10)	160.06(9)	C(7)–Fe(1)–C(11)	123.55(9)
C(7)–Fe(1)–C(12)	106.86(9)	C(8)–Fe(1)–C(9)	40.70(9)
C(8)–Fe(1)–C(10)	68.30(9)	C(8)–Fe(1)–C(11)	68.55(9)
C(8)–Fe(1)–C(12)	40.99(9)	C(9)–Fe(1)–C(10)	40.55(9)
C(9)–Fe(1)–C(11)	68.30(9)	C(9)–Fe(1)–C(12)	68.72(10)
C(10)–Fe(1)–C(11)	40.35(9)	C(10)–Fe(1)–C(12)	68.41(9)
C(11)–Fe(1)–C(12)	40.84(9)	N(1)–O(2)–C(2)	108.81(15)
Pd(1)–N(1)–O(2)	125.42(12)	Pd(1)–N(1)–C(1)	120.41(14)
O(2)–N(1)–C(1)	113.80(16)	Pd(1)–N(2)–C(13)	121.39(15)
Pd(1)–N(2)–C(17)	120.11(14)	C(13)–N(2)–C(17)	118.22(19)
Pd(1)–N(3)–C(18)	122.57(15)	Pd(1)–N(3)–C(22)	119.81(15)
C(18)–N(3)–C(22)	117.42(19)	O(1)–C(1)–N(1)	126.58(19)
O(1)–C(1)–C(4)	124.99(19)	N(1)–C(1)–C(4)	108.43(18)
O(2)–C(2)–H(2A)	109.5	O(2)–C(2)–H(2B)	109.5
O(2)–C(2)–H(2C)	109.5	H(2A)–C(2)–H(2B)	109.5
H(2A)–C(2)–H(2C)	109.5	H(2B)–C(2)–H(2C)	109.5
Pd(1)–C(3)–Fe(1)	126.04(11)	Pd(1)–C(3)–C(4)	113.69(15)
Pd(1)–C(3)–C(7)	139.70(16)	Fe(1)–C(3)–C(4)	68.56(12)
Fe(1)–C(3)–C(7)	69.22(12)	C(4)–C(3)–C(7)	106.62(18)
Fe(1)–C(4)–C(1)	120.40(15)	Fe(1)–C(4)–C(3)	70.63(12)
Fe(1)–C(4)–C(5)	70.03(12)	C(1)–C(4)–C(3)	117.46(18)
C(1)–C(4)–C(5)	132.3(2)	C(3)–C(4)–C(5)	109.91(19)
Fe(1)–C(5)–C(4)	68.92(12)	Fe(1)–C(5)–H(5)	126.8
Fe(1)–C(5)–C(6)	69.37(13)	C(4)–C(5)–H(5)	126.8
C(4)–C(5)–C(6)	106.36(19)	H(5)–C(5)–C(6)	126.8
Fe(1)–C(6)–C(5)	69.76(13)	Fe(1)–C(6)–H(6)	125.7
Fe(1)–C(6)–C(7)	69.75(13)	C(5)–C(6)–H(6)	125.7
C(5)–C(6)–C(7)	108.67(19)	H(6)–C(6)–C(7)	125.7
Fe(1)–C(7)–C(3)	70.12(12)	Fe(1)–C(7)–C(6)	69.31(13)
Fe(1)–C(7)–H(7)	125.8	C(3)–C(7)–C(6)	108.45(19)
C(3)–C(7)–H(7)	125.8	C(6)–C(7)–H(7)	125.8
Fe(1)–C(8)–H(8)	126.0	Fe(1)–C(8)–C(9)	69.84(13)
Fe(1)–C(8)–C(12)	69.44(13)	H(8)–C(8)–C(9)	126.0
H(8)–C(8)–C(12)	126.0	C(9)–C(8)–C(12)	108.01(19)
Fe(1)–C(9)–C(8)	69.47(13)	Fe(1)–C(9)–H(9)	126.0
Fe(1)–C(9)–C(10)	70.16(14)	C(8)–C(9)–H(9)	126.0
C(8)–C(9)–C(10)	108.0(2)	H(9)–C(9)–C(10)	126.0
Fe(1)–C(10)–C(9)	69.28(13)	Fe(1)–C(10)–H(10)	125.9
Fe(1)–C(10)–C(11)	69.67(13)	C(9)–C(10)–H(10)	125.9
C(9)–C(10)–C(11)	108.2(2)	H(10)–C(10)–C(11)	125.9
Fe(1)–C(11)–C(10)	69.98(13)	Fe(1)–C(11)–H(11)	126.0
Fe(1)–C(11)–C(12)	69.05(12)	C(10)–C(11)–H(11)	126.0
C(10)–C(11)–C(12)	108.1(2)	H(11)–C(11)–C(12)	126.0
Fe(1)–C(12)–C(8)	69.57(13)	Fe(1)–C(12)–C(11)	70.12(13)
Fe(1)–C(12)–H(12)	126.2	C(8)–C(12)–C(11)	107.7(2)

C(8)–C(12)–H(12)	126.2	C(11)–C(12)–H(12)	126.2
N(2)–C(13)–H(13)	118.7	N(2)–C(13)–C(14)	122.5(2)
H(13)–C(13)–C(14)	118.7	C(13)–C(14)–H(14)	120.6
C(13)–C(14)–C(15)	118.8(2)	H(14)–C(14)–C(15)	120.6
C(14)–C(15)–H(15)	120.7	C(14)–C(15)–C(16)	118.5(2)
H(15)–C(15)–C(16)	120.7	C(15)–C(16)–H(16)	120.3
C(15)–C(16)–C(17)	119.5(2)	H(16)–C(16)–C(17)	120.3
N(2)–C(17)–C(16)	122.4(2)	N(2)–C(17)–H(17)	118.8
C(16)–C(17)–H(17)	118.8	N(3)–C(18)–H(18)	118.5
N(3)–C(18)–C(19)	123.0(2)	H(18)–C(18)–C(19)	118.5
C(18)–C(19)–H(19)	120.6	C(18)–C(19)–C(20)	118.8(2)
H(19)–C(19)–C(20)	120.6	C(19)–C(20)–H(20)	120.7
C(19)–C(20)–C(21)	118.5(2)	H(20)–C(20)–C(21)	120.7
C(20)–C(21)–H(21)	120.2	C(20)–C(21)–C(22)	119.5(2)
H(21)–C(21)–C(22)	120.2	N(3)–C(22)–C(21)	122.7(2)
N(3)–C(22)–H(22)	118.7	C(21)–C(22)–H(22)	118.7
Cl(1)–C(23)–Cl(2)	110.77(15)	Cl(1)–C(23)–Cl(3)	110.65(14)
Cl(1)–C(23)–D(23)	108.4	Cl(2)–C(23)–Cl(3)	110.04(13)
Cl(2)–C(23)–D(23)	108.4	Cl(3)–C(23)–D(23)	108.4

Table 4. Anisotropic displacement parameters ($Å^2$) for hl3006. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ...+ 2hka^*b^*U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Pd(1)	0.01095(8)	0.01229(9)	0.01207(9)	0.00303(6)	0.00158(6)	0.00253(6)
Fe(1)	0.01444(15)	0.01347(16)	0.01256(16)	0.00381(12)	0.00313(11)	0.00647(13)
O(1)	0.0134(8)	0.0176(8)	0.0270(9)	0.0085(7)	0.0048(6)	0.0035(7)
O(2)	0.0196(8)	0.0121(8)	0.0192(8)	0.0061(6)	0.0013(6)	0.0052(6)
N(1)	0.0131(8)	0.0095(9)	0.0170(9)	0.0046(7)	0.0026(7)	0.0020(7)
N(2)	0.0123(8)	0.0147(9)	0.0136(9)	0.0028(7)	0.0023(7)	0.0020(7)
N(3)	0.0153(9)	0.0182(10)	0.0167(10)	0.0025(8)	0.0025(7)	0.0063(8)
C(1)	0.0151(10)	0.0151(11)	0.0097(10)	0.0023(8)	0.0029(8)	0.0046(9)
C(2)	0.0315(13)	0.0171(12)	0.0253(13)	0.0011(10)	0.0033(10)	0.0117(11)
C(3)	0.0160(10)	0.0141(11)	0.0118(10)	0.0015(8)	0.0013(8)	0.0044(9)
C(4)	0.0150(10)	0.0147(11)	0.0120(10)	0.0032(8)	0.0052(8)	0.0063(9)
C(5)	0.0190(11)	0.0197(12)	0.0159(11)	0.0030(9)	0.0063(9)	0.0109(9)
C(6)	0.0261(12)	0.0151(11)	0.0169(11)	0.0025(9)	0.0037(9)	0.0114(10)
C(7)	0.0209(11)	0.0126(11)	0.0160(11)	0.0013(9)	0.0033(9)	0.0042(9)
C(8)	0.0241(12)	0.0262(13)	0.0153(11)	0.0024(9)	0.0046(9)	0.0167(10)
C(9)	0.0280(12)	0.0182(12)	0.0157(11)	0.0003(9)	0.0040(9)	0.0114(10)
C(10)	0.0199(11)	0.0246(13)	0.0154(11)	0.0015(9)	0.0010(9)	0.0101(10)
C(11)	0.0235(12)	0.0264(13)	0.0124(11)	0.0057(9)	0.0037(9)	0.0134(10)
C(12)	0.0220(12)	0.0240(12)	0.0155(11)	0.0049(9)	0.0085(9)	0.0094(10)
C(13)	0.0215(12)	0.0229(12)	0.0148(11)	0.0035(9)	0.0042(9)	0.0030(10)
C(14)	0.0218(12)	0.0240(13)	0.0200(12)	0.0100(10)	0.0063(9)	0.0040(10)
C(15)	0.0156(11)	0.0155(11)	0.0294(13)	0.0078(10)	0.0043(9)	0.0026(9)
C(16)	0.0180(11)	0.0184(12)	0.0211(12)	–0.0013(10)	0.0020(9)	0.0012(9)
C(17)	0.0157(11)	0.0209(12)	0.0145(11)	0.0033(9)	0.0042(8)	0.0039(9)
C(18)	0.0213(12)	0.0311(14)	0.0235(13)	0.0065(11)	0.0083(10)	0.0130(11)
C(19)	0.0232(13)	0.0521(19)	0.0353(15)	0.0110(14)	0.0090(11)	0.0230(13)
C(20)	0.0298(14)	0.0447(17)	0.0322(15)	0.0090(13)	0.0020(11)	0.0269(13)
C(21)	0.0276(13)	0.0298(14)	0.0229(13)	0.0099(11)	0.0005(10)	0.0131(11)
C(22)	0.0174(11)	0.0227(12)	0.0223(12)	0.0053(10)	0.0022(9)	0.0064(10)
Cl(1)	0.0477(5)	0.0481(5)	0.0555(5)	–0.0213(4)	0.0066(4)	0.0150(4)
Cl(2)	0.0306(3)	0.0289(4)	0.0497(4)	0.0104(3)	–0.0054(3)	0.0128(3)
Cl(3)	0.0355(4)	0.0418(5)	0.0945(7)	0.0354(5)	0.0301(4)	0.0172(4)
C(23)	0.0199(12)	0.0210(13)	0.0401(15)	0.0045(11)	0.0050(10)	0.0091(10)

Table 5. Hydrogen coordinates and isotropic displacement parameters ($Å^2$) for hl3006.

	x	y	z	U
H(2A)	0.1234	–0.0053	0.1984	0.037
H(2B)	0.2159	–0.0874	0.2502	0.037
H(2C)	0.3010	0.0550	0.2075	0.037
H(5)	–0.0385	0.4130	0.2284	0.020
H(6)	0.1409	0.6599	0.1977	0.022
H(7)	0.4150	0.6831	0.2467	0.021
H(8)	0.3829	0.3147	0.0748	0.024
H(9)	0.1023	0.1503	0.0586	0.024
H(10)	–0.0582	0.2790	–0.0173	0.024
H(11)	0.1221	0.5233	–0.0476	0.024
H(12)	0.3960	0.5467	0.0097	0.024
H(13)	0.6211	0.5539	0.1836	0.026
H(14)	0.8108	0.7709	0.1809	0.028
H(15)	0.9385	0.9271	0.3389	0.025
H(16)	0.8780	0.8527	0.4950	0.026
H(17)	0.6934	0.6308	0.4906	0.022
H(18)	0.7792	0.3982	0.3481	0.029
H(19)	0.9407	0.3128	0.4352	0.041
H(20)	0.8577	0.1592	0.5546	0.039
H(21)	0.6159	0.1016	0.5838	0.032
H(22)	0.4609	0.1890	0.4912	0.026

Table 6. Torsion angles [°] for hl3006.

C(2)–O(2)–N(1)–Pd(1)	–91.72(18)	C(2)–O(2)–N(1)–C(1)	81.3(2)
Pd(1)–N(1)–C(1)–O(1)	179.27(17)	Pd(1)–N(1)–C(1)–C(4)	–1.0(2)
O(2)–N(1)–C(1)–O(1)	5.8(3)	O(2)–N(1)–C(1)–C(4)	–174.46(16)
Pd(1)–C(3)–C(4)–Fe(1)	–121.19(13)	Pd(1)–C(3)–C(4)–C(1)	–6.2(2)
Pd(1)–C(3)–C(4)–C(5)	179.62(15)	Fe(1)–C(3)–C(4)–C(1)	114.95(18)
Fe(1)–C(3)–C(4)–C(5)	–59.19(15)	C(7)–C(3)–C(4)–Fe(1)	59.01(15)
C(7)–C(3)–C(4)–C(1)	173.96(18)	C(7)–C(3)–C(4)–C(5)	–0.2(2)
O(1)–C(1)–C(4)–Fe(1)	–93.0(2)	O(1)–C(1)–C(4)–C(3)	–175.6(2)
O(1)–C(1)–C(4)–C(5)	–3.1(4)	N(1)–C(1)–C(4)–Fe(1)	87.3(2)
N(1)–C(1)–C(4)–C(3)	4.7(3)	N(1)–C(1)–C(4)–C(5)	177.2(2)
Fe(1)–C(4)–C(5)–C(6)	–59.55(15)	C(1)–C(4)–C(5)–Fe(1)	–113.4(2)
C(1)–C(4)–C(5)–C(6)	–173.0(2)	C(3)–C(4)–C(5)–Fe(1)	59.55(15)
C(3)–C(4)–C(5)–C(6)	0.0(3)	Fe(1)–C(5)–C(6)–C(7)	–59.07(16)
C(4)–C(5)–C(6)–Fe(1)	59.26(15)	C(4)–C(5)–C(6)–C(7)	0.2(3)
Pd(1)–C(3)–C(7)–Fe(1)	121.7(2)	Pd(1)–C(3)–C(7)–C(6)	–179.42(19)
Fe(1)–C(3)–C(7)–C(6)	58.89(15)	C(4)–C(3)–C(7)–Fe(1)	–58.59(15)
C(4)–C(3)–C(7)–C(6)	0.3(2)	Fe(1)–C(6)–C(7)–C(3)	–59.39(15)
C(5)–C(6)–C(7)–Fe(1)	59.08(16)	C(5)–C(6)–C(7)–C(3)	–0.3(3)
Fe(1)–C(8)–C(9)–C(10)	59.80(16)	C(12)–C(8)–C(9)–Fe(1)	–59.15(16)
C(12)–C(8)–C(9)–C(10)	0.6(3)	Fe(1)–C(9)–C(10)–C(11)	58.95(16)
C(8)–C(9)–C(10)–Fe(1)	–59.36(16)	C(8)–C(9)–C(10)–C(11)	–0.4(3)
Fe(1)–C(10)–C(11)–C(12)	58.73(16)	C(9)–C(10)–C(11)–Fe(1)	–58.71(16)
C(9)–C(10)–C(11)–C(12)	0.0(3)	Fe(1)–C(11)–C(12)–C(8)	59.69(15)
C(10)–C(11)–C(12)–Fe(1)	–59.31(16)	C(10)–C(11)–C(12)–C(8)	0.4(3)
Fe(1)–C(8)–C(12)–C(11)	–60.03(16)	C(9)–C(8)–C(12)–Fe(1)	59.40(16)
C(9)–C(8)–C(12)–C(11)	–0.6(3)	Pd(1)–N(2)–C(13)–C(14)	173.81(18)
C(17)–N(2)–C(13)–C(14)	0.0(3)	N(2)–C(13)–C(14)–C(15)	–1.5(4)
C(13)–C(14)–C(15)–C(16)	1.7(4)	C(14)–C(15)–C(16)–C(17)	–0.5(3)
Pd(1)–N(2)–C(17)–C(16)	–172.54(17)	C(13)–N(2)–C(17)–C(16)	1.4(3)
C(15)–C(16)–C(17)–N(2)	–1.1(4)	Pd(1)–N(3)–C(18)–C(19)	175.9(2)
C(22)–N(3)–C(18)–C(19)	1.1(4)	N(3)–C(18)–C(19)–C(20)	–0.5(4)
C(18)–C(19)–C(20)–C(21)	–0.7(4)	C(19)–C(20)–C(21)–C(22)	1.2(4)
Pd(1)–N(3)–C(22)–C(21)	–175.47(19)	C(18)–N(3)–C(22)–C(21)	–0.5(4)
C(20)–C(21)–C(22)–N(3)	–0.6(4)		

Table 7. Hydrogen bonds for hl3006 [Å and °].

D–H...A	d(D–H)	d(H...A)	d(D...A)	<(DHA)